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(54) AMINOCYCLOHEXYLESTERS AND USES THEREOF

AMINOCYCLOHEXYLESTER UND IHRE ANWENDUNG

AMINOCYCLOHEXYLESTERS ET LEURS UTILISATIONS

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(56) References cited:

FR-A-2 689 893 US-A-2 954 380

- J. MED. CHEM. vol. 32, 1989, pages 1620 - 1626

Description**Technical Field**

5 [0001] The present invention is generally directed toward aminocyclohexylester compounds, including thioesters, for use in cardiac arrhythmias and the preparation of pharmaceutical compositions and kits.

Background of the Invention

10 [0002] Arrhythmia is a variation from the normal rhythm of the heart beat. The major cause of fatalities due to cardiac arrhythmias is the subtype of arrhythmias known as ventricular fibrillation. Conservative estimates indicate that, in the U.S. alone, approximately 300,000 individuals per year suffer heart attacks. Approximately half of these die from sudden cardiac death, the major cause of which is ventricular fibrillation.

15 [0003] Antiarrhythmic agents have been developed to prevent or alleviate cardiac arrhythmia. For example, Class I antiarrhythmic compounds have been used to treat supraventricular arrhythmias and ventricular arrhythmias. Treatment of ventricular arrhythmia is very important since such an arrhythmia, especially ventricular fibrillation, can be fatal. Serious ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) occur most often in the presence of myocardial ischemia and/or infarction. Ventricular fibrillation often occurs in the setting of acute myocardial ischemia, before infarction fully develops. At present, lidocaine is the current drug of choice for prevention of ventricular fibrillation.

20 However, many Class I antiarrhythmic compounds may actually increase mortality in patients who have had a myocardial infarction. Therefore, there is a need in the art to identify new antiarrhythmic treatments, particularly treatments for ventricular arrhythmias. The present invention fulfills this need, and further provides other related advantages.

[0004] US-A-2 954 380 discloses piperzinocyclohexyl esters useful as CNS depressants and hypotensive agents.
 [0005] J. Med. Chem., Vol 32, 1989, p 1620-1626 discloses certain opioid analgesics.

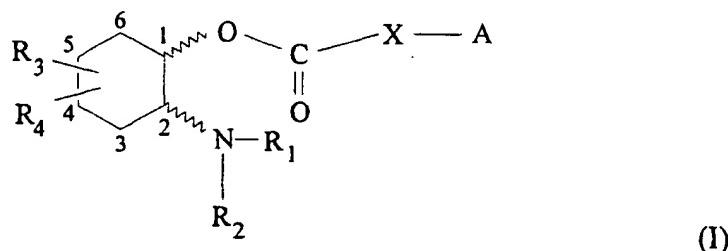
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Summary of the Invention

[0006] Briefly stated, the present invention provides compounds for a variety of uses, including the blockade of ion channels *in vitro* and *in vivo*, and for the treatment of arrhythmias.

30 [0007] In an aspect of the present invention, aminocyclohexyl esters and thioesters are provided. In one embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

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wherein X is a direct bond;

or $-(CH_2)_n-Y-$, where n = 1, 2, or 3, and Y is a direct bond, O or S;

or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S;

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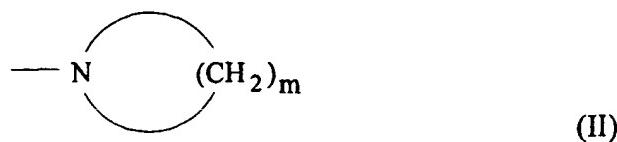
or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

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or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring denoted by formula II:

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where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

15

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

20

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

25

R_3 and R_4 are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII:

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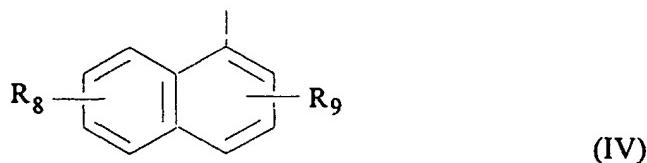


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where R_5 , R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl, and when X is a direct bond at least one of R_5 , R_6 and R_7 is a hydroxy, fluorine, chlorine, bromine, trifluoromethyl, alkyl of from one to six carbon atoms, or aryl substituent, and when X is -CH=CH-, and R_1 and R_2 when taken together with the nitrogen atom to which they are attached, form a N-phenylpiperazine ring, and R_3 and R_4 are hydrogen, at least one of R_5 , R_6 and R_7 is a substituent other than hydrogen;

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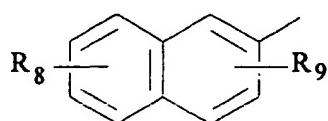


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where R_8 and R_9 are independently hydrogen, hydroxy, fluorine, chlorine, bromine; alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

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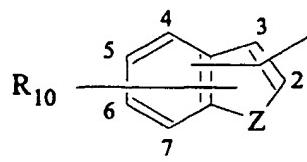


(V)

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where R₈ and R₉ are defined as above;

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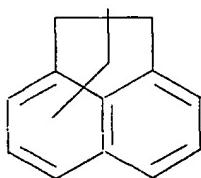


(VI)

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where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

25

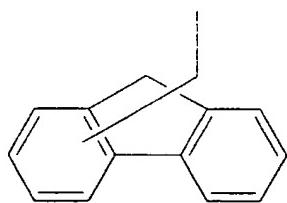


(VII)

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only when X is a direct bond;

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(VIII)

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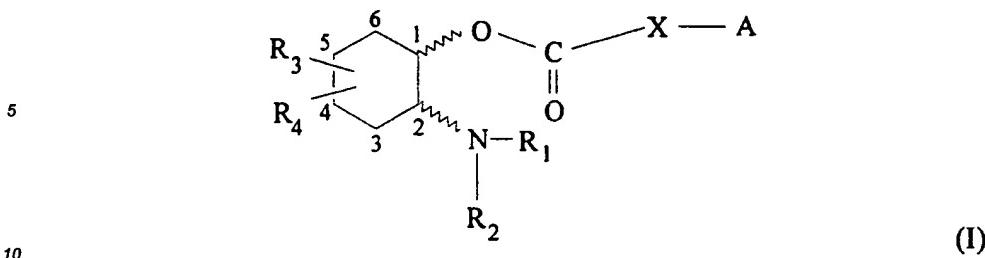
only when X is a direct bond;

50

with the proviso that, when X is -(CH₂)_n-Y-, and n = 1, and Y is a direct bond, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthyl.

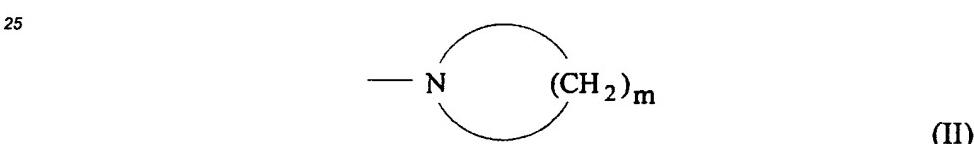
[0008] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

55



wherein X is a direct bond;

- 15 or $-(CH_2)_n-Y-$, where $n = 1$ and Y is a direct bond, O or S;
 or $-CH(R_{12})-$, where R_{12} is alkyl of from one to six carbon atoms;
 or $-C(R_{13})=CH-$, where R_{13} is hydrogen;
- 20 R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;
- or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring denoted by formula II:



- where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;
- 35 or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;
- 40 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

45 R_3 and R_4 are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

50 A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from:

- formula III where R_5 , R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl, and when X is a direct bond at least one of R_5 , R_6 and R_7 is a hydroxy, fluorine, chlorine, bromine, trifluoromethyl, alkyl of from one to six carbon atoms, or aryl substituent, and when X is $-CH=CH-$, and R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a N-phenylpiperazine ring, and R_3 and R_4 are hydrogen, at least one of R_5 , R_6 and R_7 is a substituent other than hydrogen;

or formula IV where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

5 or formula V where R₈ and R₉ are defined as above;

10 or formula VI where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

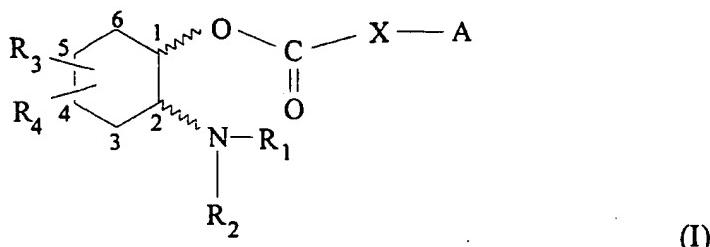
15 or formula VII only when X is a direct bond;

20 or formula VIII only when X is a direct bond;

with the proviso that, when X is -(CH₂)_n-Y-, and n = 1, and Y is a direct bond, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthetyl.

[0009] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

20



30 wherein X is -(CH₂)_n-Y-, where n = 1 and Y is a direct bond or O; or -CH(R₁₂)-, where R₁₂ is alkyl of from one to six carbon atoms;

35 R₁ and R₂ are defined as in formula I as first described herein;

R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

40 A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from:

formula III where R₅, R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl;

45 or formula IV where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

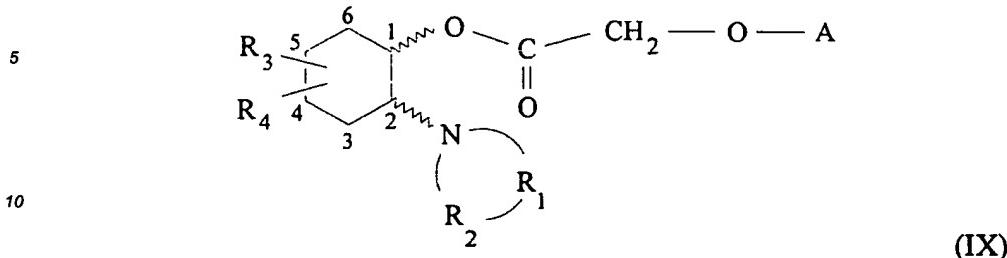
or formula V where R₈ and R₉ are defined as above;

50 or formula VI where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

55 with the proviso that, when X is -(CH₂)_n-Y-, and n = 1, and Y is a direct bond, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthetyl.

[0010] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula

IX, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:



15 wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached, either form a ring according to formula II, where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

20 or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring forming atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

25 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

30 R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring; and

A is a saturated carbocyclic ring of three to six carbon atoms, or is selected from:

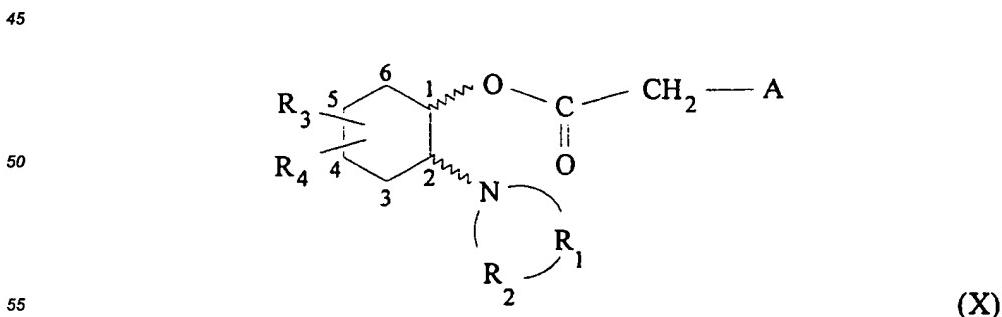
35 formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;

or formula IV where R₈ and R₉ are hydrogen;

or formula V where R₈ and R₉ are hydrogen;

40 or formula VI where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl.

[0011] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula X, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:



wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring denoted

as in formula II, where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

- 5 or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;
- 10 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

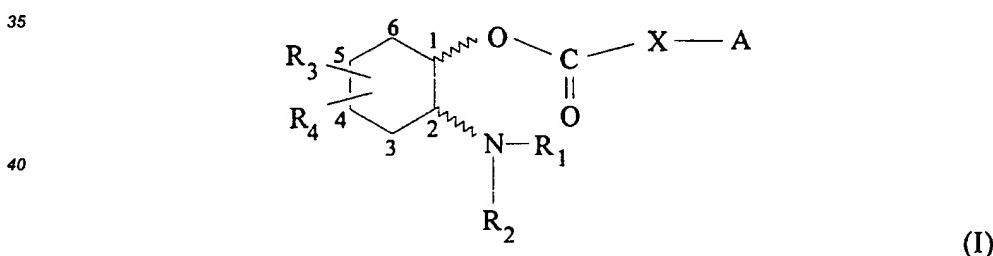
R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring; and

15 A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

- 20 formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;
- 25 or formula IV where R₈ and R₉ are hydrogen;
- 30 or formula V where R₈ and R₉ are hydrogen;
- 35 or formula VI where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl;

with the proviso that when R₁ and R₂, taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthetyl.

[0012] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:



45 wherein X is a direct bond or -CH=CH-;

R₁ and R₂ are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

- 50 or R₁ and R₂, when taken together with the nitrogen atom to which they are attached,
- 55 form a ring denoted by formula II where m is an integer from three to eight;
- 60 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

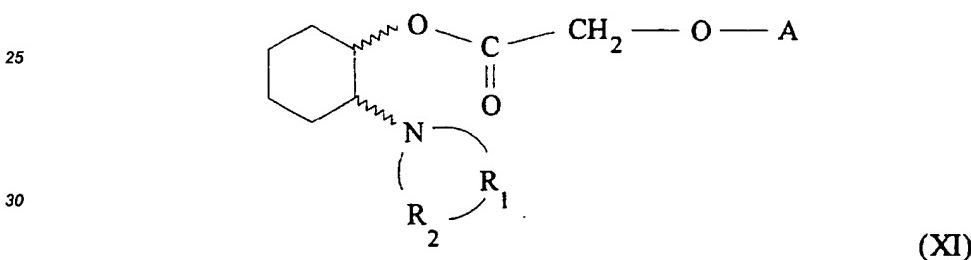
R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently

hydrogen, methoxy, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

- 5 formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, methyl or ethyl, and at least one of R₆ and R₇ is a substituent other than hydrogen;
- 10 or formula IV where R₈ and R₉ are hydrogen;
- 15 or formula V where R₈ and R₉ are hydrogen;
- or formula VI where R₁₀ is hydrogen, and Z is O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl;
- 20 or formula VII when X is a direct bond;
- or formula VIII when X is a direct bond.

[0013] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XI, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:



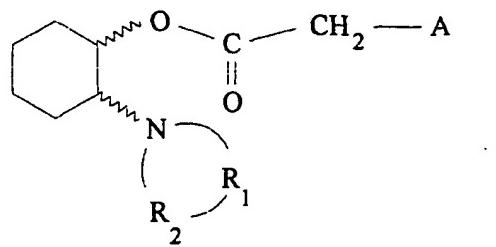
35 wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring according to formula II where m is an integer from three to eight; and

A is selected from:

- 40 formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;
- or formula IV where R₈ and R₉ are hydrogen;
- 45 or formula V where R₈ and R₉ are hydrogen;
- or formula VI where R₁₀ is hydrogen, and Z is O or S.

[0014] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XII, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

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wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring according to formula II where m is an integer from three to eight; and

15

A is selected from:

20

formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;

or formula IV where R₈ and R₉ are hydrogen;

25

or formula V where R₈ and R₉ are hydrogen;

or formula VI where R₁₀ is hydrogen, and Z is O or S;

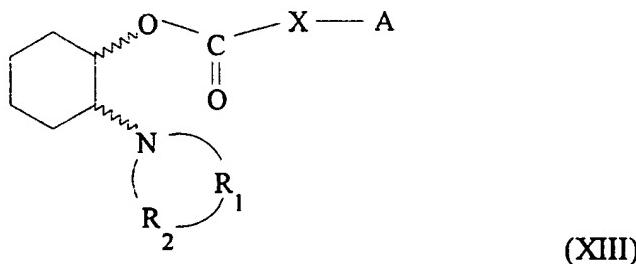
with the proviso that, when R₁ and R₂ taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring, A may not be 4-thianaphthetyl.

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[0015] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XIII, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

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wherein X is a direct bond, trans-CH=CH-, -CH₂- or -CH₂-O-;

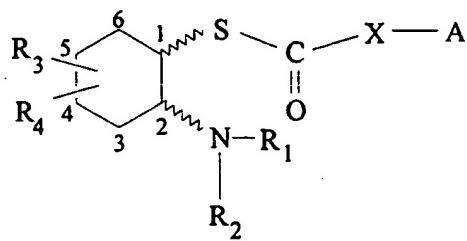
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R₁ and R₂, when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, piperidinyl, hexahydroazepinyl, morpholinyl, methylpiperazinyl or 3-azabicyclo[3.2.2]nonanyl; and A is selected from cyclohexyl, 3,4-dichlorophenyl, 4-bromophenyl, 1-naphthyl, 2-naphthyl or 3-thianaphthetyl.

[0016] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XIV, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

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(XIV)

wherein X is a direct bond;

or $-(CH_2)_n-Y-$, where $n = 1, 2$, or 3 , and Y is a direct bond, O or S;

15

or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S;

or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

20

R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring denoted by formula II:

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(II)

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where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

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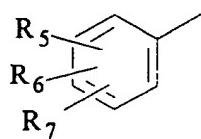
or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

50

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII:

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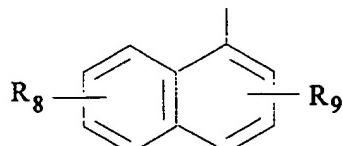


(III)

EP 0 720 605 B1

where R₅, R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl, and when X is a direct bond at least one of R₅, R₆ and R₇ is a substituent other than hydrogen;

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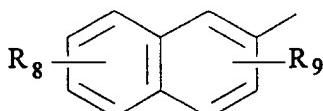


(IV)

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where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

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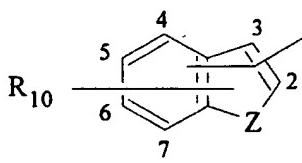


(V)

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where R₈ and R₉ are defined as above;

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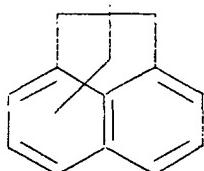
(VI)

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where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

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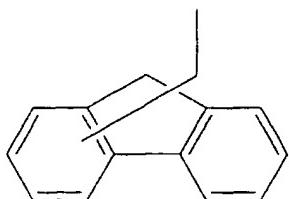
(VII)

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only when X is a direct bond;

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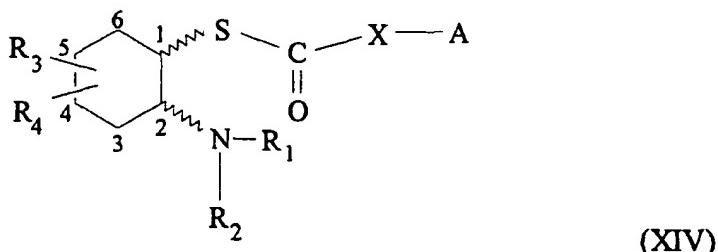
(VIII)

only when X is a direct bond.

[0017] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XIV, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

5

10



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wherein X is a direct bond;

or $-(CH_2)_n-Y-$, where $n = 1$, and Y is a direct bond, O or S;

or $-CH(R_{12})-$, where R_{12} is alkyl of from one to six carbon atoms;

or $-C(R_{13})=CH-$, where R_{13} is hydrogen;

20

R_1 and R_2 are defined as in formula XIV as first described herein;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

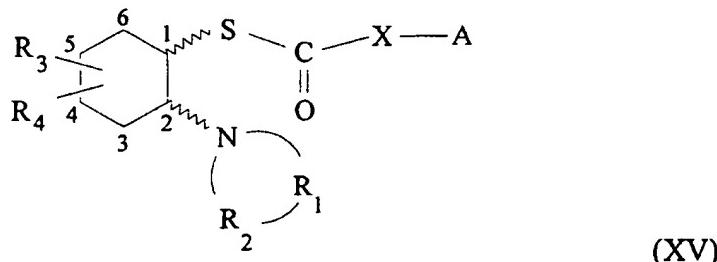
A is defined as in formula XIV as first described herein.

25

[0018] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XV, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

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wherein X is a $-CH_2-$ or $-CH_2-O-$;

R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring according to formula II, where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

50

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring forming atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

55

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring; and

A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

5

formula III where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy;

or formula IV where R_8 and R_9 are hydrogen;

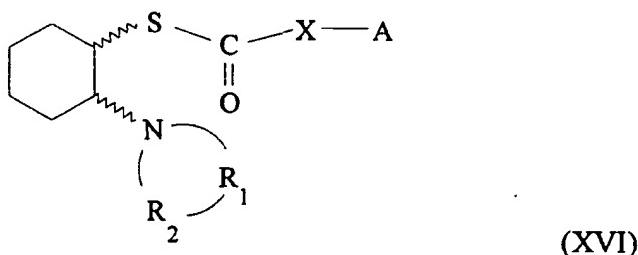
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or formula V where R_8 and R_9 are hydrogen;

or formula VI where R_{10} is hydrogen, and Z is CH_2 , O, S, or $\text{N}-\text{R}_{11}$ where R_{11} is hydrogen or methyl.

15 [0019] In another embodiment, a compound comprises an enantiomer or geometric isomer of a compound of formula XVI, or a solvate or pharmaceutically acceptable salt thereof, the compound of the formula:

20



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wherein X is a $-\text{CH}_2-$ or $-\text{CH}_2-\text{O}-$;

R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring according to formula II where m is an integer from three to eight; and

35

A is selected from:

formula III where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy;

40

or formula IV where R_8 and R_9 are hydrogen;

or formula V where R_8 and R_9 are hydrogen;

or formula VI where R_{10} is hydrogen, and Z is O or S.

45

[0020] In another aspect of the present invention, compositions are provided that comprise an aminocyclohexyl ester or thioester compound described above in combination with a pharmaceutically acceptable carrier or diluent.

[0021] The present invention, in another aspect, provides the compounds described above for use in a method for treating arrhythmia in a warm-blooded animal, and for use in methods for blocking ion channels *in vivo* and *in vitro*.

50

[0022] In yet another aspect of the present invention, compounds including those described above are provided for the manufacture of a medicament for the treatment of arrhythmia.

[0023] These and other aspects of the present invention will become evident upon reference to the following detailed description.

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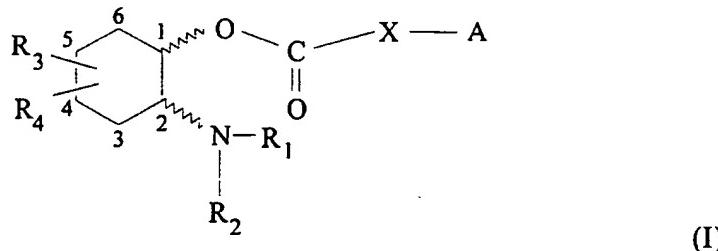
Detailed Description of the Invention

[0024] As noted above, the present invention is directed toward aminocyclohexyl ester and thioester compounds which have a variety of uses. Such uses include blockade of ion channels *in vitro* and *in vivo*, and the treatment of

arrhythmias.

[0025] In one aspect, the compounds of the present invention are esters which may be represented by formula I:

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Compounds of formula I are aminocyclohexyl ester compounds. More specifically, these aminocyclohexyl esters are substituted at position 2 of the cyclohexyl ring with an amino group, NR₁R₂. The cyclohexyl ring may also be substituted with additional substituents (designated as R₃ and R₄) as described in more detail below. Examples of specific embodiments of the elements of compounds represented by formula I include the following.

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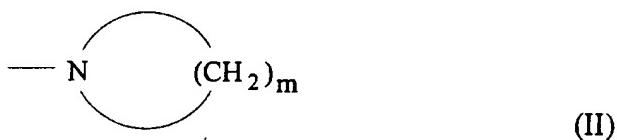
[0026] Depending upon the selection of substituents R₁ and R₂, the compounds of formula I may be primary, secondary, or tertiary amines (i.e., where R₁ and R₂ both are hydrogen, or only one is hydrogen, or neither are hydrogen, respectively). Where the amine is tertiary, it may be a cyclic amine. Amino substituents R₁ and R₂ may be independently selected from substituents which include hydrogen, alkyl groups containing from three to eight carbon atoms, alkoxyalkyl groups containing from three to eight carbon atoms, and aralkyl groups containing from seven to twelve carbon atoms. As used herein, the term "alkyl group" refers to branched or unbranched saturated hydrocarbon fragments containing the specified number of carbon atoms. Examples include n-propyl, isopropyl, and t-butyl. As used herein, the term "alkoxyalkyl" refers to alkyl groups substituted with alkoxy groups which in turn are alkyl groups attached to an oxygen atom. For example, a methoxyethyl group (CH₃OCH₂CH₂-) is a three carbon alkoxyalkyl group. As used herein, the term "aralkyl" refers to alkyl groups substituted with aryl groups. Aryl groups are unsubstituted aromatic groups, with phenyl and naphthyl groups preferred. An example of an aralkyl group is the benzyl group (C₆H₅CH₂-) which is a seven carbon aralkyl group.

25

[0027] Alternatively, R₁ and R₂, when taken together with the amino nitrogen atom, may form a ring represented by formula II:

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where m is an integer from three to eight. Additionally, the ring carbon atoms may be also substituted. Suitable substituents include hydroxy, oxo (=O), alkyl groups containing from one to three carbon atoms, and alkoxy groups containing from one to three carbon atoms. The ring may also be fused at two adjacent carbon atoms with a second ring. The second ring may be either an aromatic ring preferably containing either five or six carbon atoms, or an aliphatic carbocycle preferably containing either five or six carbon atoms. Examples of amino substituents containing a fused ring system as described include perhydroindolyl and 1,2,3,4-tetrahydroisoquinolinyl groups.

45

[0028] In addition to R₁ and R₂ forming a chain of ring carbon atoms, R₁ and R₂, when taken together with the nitrogen atom to which they are attached, may complete a saturated monocyclic ring of from five to eight ring atoms which includes additional heteroatoms. Preferably, R₁ and R₂, when taken together, contain only a single heteroatom. Preferred heteroatoms include nitrogen and oxygen. An example of a ring in which R₁ and R₂ together include oxygen as a ring atom is the morpholinyl group. An example of a ring where R₁ and R₂ together include nitrogen as a ring atom is the piperazinyl group. For cyclohexyl esters of formula I which are substituted at position 2 with a heterocyclic ring containing two nitrogen ring atoms, the nitrogen of R₁ and R₂ (i.e., the nitrogen ring atom not attached to the cyclohexyl ring) may be further substituted. Suitable substituents include phenyl and alkyl groups containing from one to six carbon atoms. Examples of such N-phenyl or N-alkyl substitution include N-phenylpiperazinyl and N-methyl-piperazinyl, respectively.

[0029] Alternatively, R₁ and R₂, when taken together with the 2-amino nitrogen of formula I, may complete a bicyclic ring. Bicyclic rings include, for example, 3-azabicyclo[3.2.2]nonane, 2-azabicyclo[2.2.2]octane, 3-azabicyclo[3.1.0]hexane, and 3-azabicyclo[3.2.0]heptane. For these derivatives, the 2-substituents of the cyclohexyl esters of formula I are the following groups: 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl.

[0030] Cyclohexane substituents R₃ and R₄ may be independently attached to ring positions 3, 4, 5 or 6 (i.e., both R₃ and R₄ may be attached to the same ring position or each attached to different ring positions). R₃ and R₄ are independently selected from substituents which include hydrogen, hydroxy, alkyl groups containing from one to six carbon atoms, alkoxy groups containing from one to six carbon atoms, or points of attachment of a spiro five- or six-membered heterocyclic ring. Preferred heterocyclic substituents contain either a single oxygen or a single sulfur ring atom.

[0031] Depending upon the nature of X, the ester side chain, -X-A in formula I above, may take several forms. A compound of formula I may have X as a direct bond. Alternatively, X may be an alkylene moiety, -(CH₂)_n, where n = 1, 2 or 3, and Y is a direct bond, an oxygen atom, or a sulfur atom; an alkylidene moiety, -CH(R₁₂)-Y-, where R₁₂ is an alkyl group of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms (including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), a phenyl group, or a benzyl group, and Y is a direct bond, an oxygen atom, or a sulfur atom; or a cis- or trans-alkenyl moiety, -C(R₁₃)=CH-, where R₁₃ is a hydrogen, an alkyl group of from one to six carbon atoms, or a phenyl group. For compounds of formula I when X is an alkenyl moiety, X is preferably a trans-alkenyl moiety.

[0032] Ester side chain component A is generally a hydrophobic moiety. Typically, a hydrophobic moiety is comprised of non-polar chemical groups such as hydrocarbons, hydrocarbons substituted with halogens, and ethers. Suitable hydrocarbons include aliphatic and aromatic hydrocarbons. Preferred aliphatic hydrocarbons include alkyl groups containing from five to twelve carbon atoms and carbocyclic groups containing from three to six carbon atoms. Preferred aromatic groups include phenyl, 1-naphthyl, 2-naphthyl, indenyl (including indene where Z, in formula VI below, is CH₂, indole where Z is N-R₁₁, benzofuran where Z is O, and thianaphthene where Z is S), acenaphthyl, and fluorenyl derivatives and are represented by formulae III, IV, V, VI, VII or VIII, respectively. As described below, in a preferred embodiment, Z is O, S or N-R₁₁, and in a particularly preferred embodiment Z is O or S.

[0033] Phenyl groups within the compounds of the present invention are represented by formula III:

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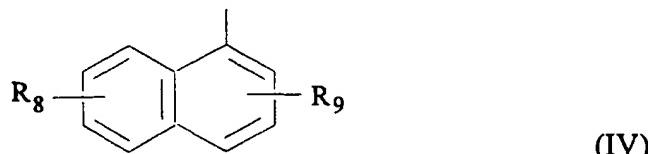
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R₅, R₆, and R₇ are independently selected from substituents which include hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl groups containing from one to six carbon atoms, alkoxy groups containing from one to six carbon atoms, or aryl groups. For compounds of formula I when X is a direct bond, at least one of R₅, R₆, and R₇ is a hydroxy, fluorine, chlorine, bromine, trifluoromethyl, alkyl of from one to six carbon atoms, or aryl substituent. For compounds of formula I when X is a -CH=CH-, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a N-phenylpiperazine ring, and R₃ and R₄ are hydrogen, at least one of R₅, R₆ and R₇ is a substituent other than hydrogen.

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[0034] 1-Naphthyl groups within the compounds of the present invention are represented by formula IV:

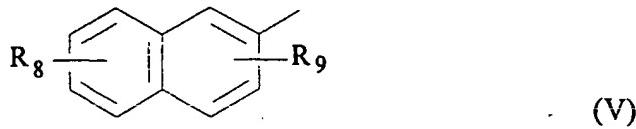
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R₈ and R₉ are independently selected from substituents which include hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl groups containing from one to six carbon atoms, alkoxy groups containing from one to six carbon atoms, or aryl groups.

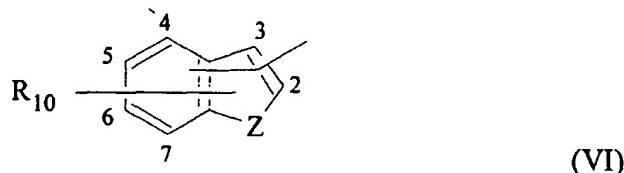
[0035] 2-Naphthyl groups within the compounds of the present invention are represented by formula V:



R₈ and R₉ are as defined above.

[0036] Indenyl groups of the present invention are represented by formula VI:

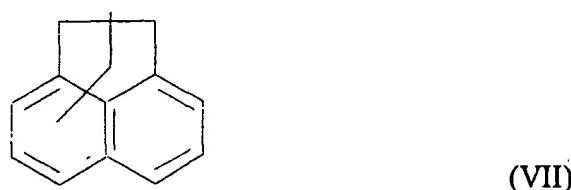
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20 R₁₀ is selected from substituents which include hydrogen, hydroxy, fluorine, chlorine, bromine, an alkyl group containing from one to six carbon atoms, an alkoxy group containing from one to six carbon atoms, or an aryl group. Z is methylene (CH₂), an oxygen atom, sulfur atom, or nitrogen atom bearing a substituent R₁₁. The indenyl groups of formula VI are derivatives of indene, indole, benzofuran, and thianaphthene when Z is methylene, nitrogen, oxygen, and sulfur, respectively. Nitrogen substituent R₁₁ may be hydrogen or an alkyl group containing from one to six carbon atoms. For compounds of formula I when X is -(CH₂)_n-Y, and n = 1, and Y is a direct bond, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthyl.

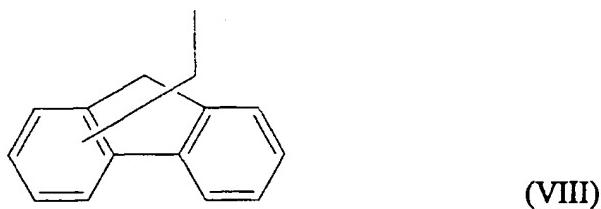
25 [0037] Acenaphthyl groups within the compounds of the present invention are represented by formula VII:

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[0038] Fluorenyl groups within the compounds of the present invention are represented by formula VIII:

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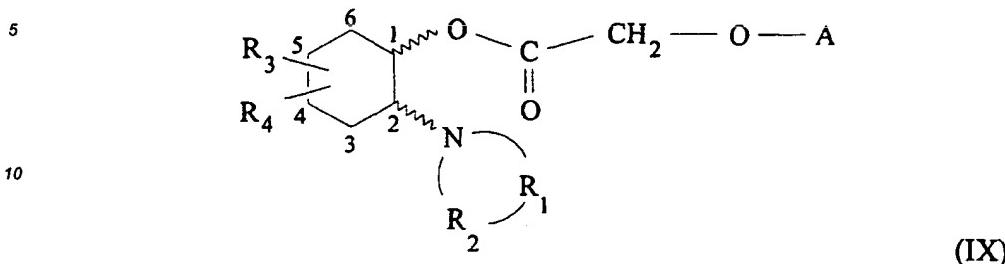


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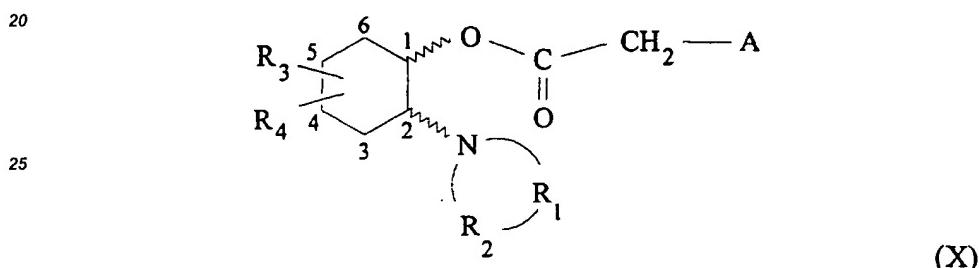
Ester side chain component A may be an acenaphthyl or fluorenyl group only when X is a direct bond. In a preferred embodiment, the acenaphthyl group is a 1-acenaphthyl group, and the fluorenyl group is a 9-fluorenyl group.

[0039] As mentioned above, the present invention provides aminocyclohexyl esters represented by formula I. In a preferred embodiment, where X is -(CH₂)_n-Y, n is 1. For these embodiments, Y is a direct bond, an oxygen atom, or a sulfur atom. In a particularly preferred embodiment, Y is a direct bond or an oxygen atom. In a preferred embodiment, where X is -CH(R₁₂)-, R₁₂ is an alkyl group from one to six carbon atoms. In a preferred embodiment, where X is -C(R₁₃)=CH-, R₁₃ is a hydrogen atom. For these embodiments, R₃ and R₄ are preferably independently attached to the cyclohexane ring at the 4- or 5- positions.

[0040] In a preferred embodiment where X is $-(\text{CH}_2)_n-\text{Y}$, where n = 1 and Y is an oxygen atom, and R₁ and R₂ are included in a ring, the present invention provides aminocyclohexyl esters represented by formula IX:



15 [0041] In a preferred embodiment where X is $-(\text{CH}_2)_n-\text{Y}$, where n = 1 and Y is a direct bond, and R₁ and R₂ are included in a ring as described above, the present invention provides aminocyclohexyl esters represented by formula X:

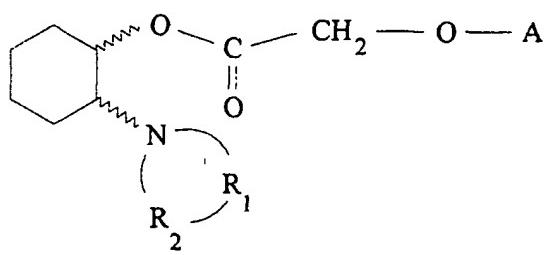


30 For either formula IX or X, R₃ and R₄ are preferably independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from substituents which include hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring. Similarly, for either formula IX or X, A is preferably a saturated carbocyclic ring of from three to six carbon atoms, or is selected from: formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen; or formula IV where R₈ and R₉ are hydrogen; or formula V where R₈ and R₉ are hydrogen; or formula VI where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl. However, for compounds represented by formula X, when R₁ and R₂, taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthényl.

35 [0042] In a preferred embodiment where X is a direct bond or -CH=CH-, the present invention provides aminocyclohexyl esters represented by formula I. For these embodiments, R₁ and R₂ are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms; or R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring denoted by formula II where m is an integer from three to eight; or R₁ and R₂ complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl. R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom. A is a saturated carbocyclic ring of from three to six carbon atoms or is selected from: formula III where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, methyl, and ethyl, and at least one of R₆ and R₇ is a substituent other than hydrogen; or formula IV where R₈ and R₉ are hydrogen; or formula V where R₈ and R₉ are hydrogen; or formula VI where R₁₀ is hydrogen, and Z is O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl; or formula VII when X is a direct bond; or formula VIII when X is a direct bond.

40 [0043] In a preferred embodiment where X is $-(\text{CH}_2)_n-\text{Y}$, where n = 1 and Y is an oxygen atom, R₁ and R₂ are included in a ring, and there are no R₃ and R₄, the present invention provides aminocyclohexyl esters represented by formula XI:

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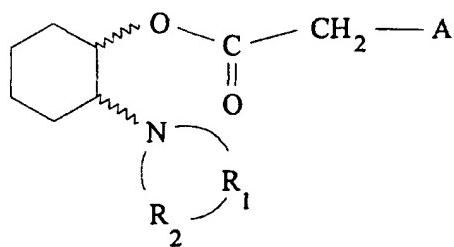
(XI)

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[0044] In a preferred embodiment where X is $-(CH_2)_n-Y$, where $n = 1$ and Y is a direct bond, R_1 and R_2 are included in a ring, and there are no R_3 and R_4 , the present invention provides aminocyclohexyl esters represented by formula XII:

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(XII)

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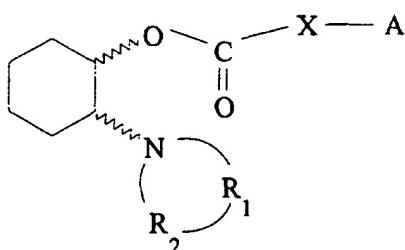
For either formula XI and XII, R_1 and R_2 preferably are taken together with the nitrogen atom to which they are attached to form a ring according to formula II where m is an integer from three to eight. Similarly, for either formula XI or XII, A is preferably selected from: formula III where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R_6 and R_7 is a substituent other than hydrogen; or formula IV where R_8 and R_9 are hydrogen; or formula V where R_8 and R_9 are hydrogen; or formula VI where R_{10} is hydrogen, and Z is O or S.

35

[0045] In a preferred embodiment where X is selected from a direct bond; $trans-C(R_{13})=CH-$ where R_{13} is a hydrogen atom; or $-(CH_2)_n-Y$ where $n = 1$ and Y is a direct bond or an oxygen atom, R_1 and R_2 are included in a ring, and there are no R_3 and R_4 , the present invention provides aminocyclohexyl esters represented by formula XIII:

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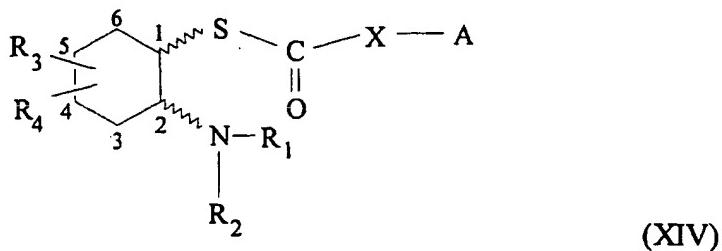


(XIII)

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R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, piperidinyl, hexahydroazepinyl, morpholinyl, methylpiperazinyl or 3-azabicyclo[3.2.2]nonanyl. A is preferably selected from 3,4-dichlorophenyl, 1-naphthyl, 2-naphthyl, cyclohexyl, 4-bromophenyl, or 3-thianaphthyl. In a preferred embodiment, the stereochemistry is the trans-configuration. In another preferred embodiment, the stereochemistry is the cis-configuration.

[0046] In another aspect, the compounds of the present invention are aminocyclohexyl thioesters which may be represented by formula XIV:



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X, R₁, R₂, R₃, R₄ and A are defined as for formula I as first described herein, except that where X is -(CH₂)_n-Y-, and n = 1, and Y is a direct bond, and R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may be 4-thianaphthenyl.

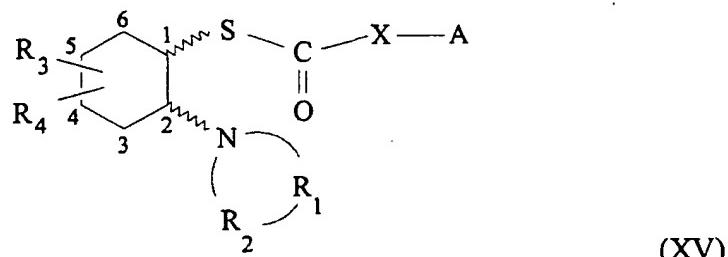
15 [0047] In a preferred embodiment where X is selected from a direct bond; -(CH₂)_n-Y- where n = 1, and Y is a direct bond, an oxygen atom, or a sulfur atom; or -CH(R₁₂)- where R₁₂ is an alkyl group of from one to six carbon atoms; or -C(R₁₃)-CH- where R₁₃ is hydrogen; the present invention provides aminocyclohexyl thioesters represented by formula XIV. R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, alkoxy of from one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom. A is preferably an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of from three to six carbon atoms, or is preferably selected from: formula III where R₅, R₆, and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl, and when X is a direct bond at least one of R₅, R₆ and R₇ is a substituent other than hydrogen; or formula IV where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl; or formula V where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl; or formula VI where R₁₀ is independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl; and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms; or formula VII when X is a direct bond; a formula VIII when X is a direct bond.

20

25

[0048] In a preferred embodiment, where X is a -(CH₂)_n-Y-, and n = 1, and Y is a direct bond or an oxygen atom, and R₁ and R₂ are included in a ring, the present invention provides aminocyclohexyl thioesters represented by formula XV.

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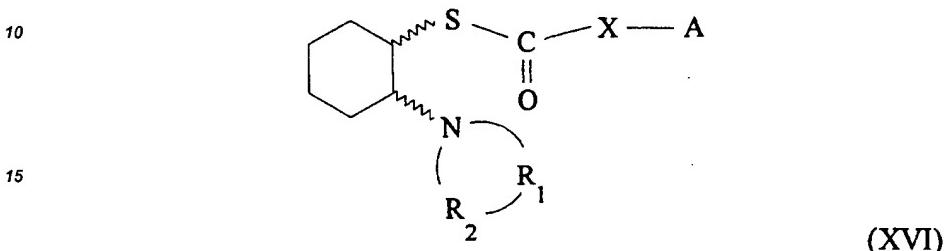


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R₁ and R₂ are preferably taken together with the nitrogen atom to which they are attached to form a ring according to formula II, where m is an integer from three to eight, and the ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of five to six carbon atoms; or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and the heterocyclic ring containing not more than two nitrogen ring forming atoms, wherein the second nitrogen is optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring; or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl. R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring. A is preferably a saturated carbocyclic ring of from three to six carbon atoms, or is preferably selected from: formula III where R₅ is hydrogen, and

R_6 and R_7 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy; or formula IV where R_8 and R_9 are hydrogen; or formula V where R_8 and R_9 are hydrogen; or formula VI where R_{10} is hydrogen, and Z is CH_2 , O, S, or N- R_{11} where R_{11} is hydrogen or methyl.

[0049] In a preferred embodiment where X is $-(CH_2)_n-Y-$, and n = 1, and Y is a direct bond or an oxygen atom, R_1 and R_2 are included in a ring, and there are no R_3 and R_4 , the present invention provides aminocyclohexyl thioesters represented by formula XVI:



20 R_1 and R_2 are preferably taken together with the nitrogen atom to which they are attached to form a ring according to formula II where m is an integer from three to eight. A is preferably selected from: formula III where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy; or formula IV where R_8 and R_9 are hydrogen; or formula V where R_8 and R_9 are hydrogen; or formula VI where R_{10} is hydrogen, and Z is O or S.

25 [0050] In the formulae depicted above, a bond to a substituent and/or a bond that links A with the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the substituent may be attached at any one of the carbon atoms in the ring structure.

30 [0051] The wavy line bonds in the above formulae indicate that the substituents at positions 1 and 2 of the cyclohexane ring may be disposed in a *cis* or *trans* relationship. The substituents R_3 and R_4 may also be independently attached *cis* or *trans* to the 2-amino substituent. The compounds of the present invention contain at least two asymmetric carbon atoms and thus exist as enantiomers and diastereomers. Unless otherwise noted, the present invention includes all enantiomeric and diastereomeric forms of the compounds of the above formulae. Pure stereoisomers, mixtures of enantiomers and/or diastereomers, and mixtures of different compounds of the above formulae are included within the present invention.

35 [0052] The compounds of the above formulae may be prepared using known synthetic methodology. In general, compounds of the present invention are prepared by reacting the appropriate 1,2-aminocyclohexanol or 1,2-aminocyclohexanethiol with an appropriate carboxylic acid derivative, derived from A-X-COOH. The carboxylic acid may be converted to a reactive intermediate such as the acid chloride by treatment with, for example, thionyl chloride. The reaction between the acid chloride and the alcohol or thiol is carried out in a suitable solvent, such as chloroform. The reaction temperature may be dependent upon the nature of the reactants, however, in general, the reaction may be refluxed. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified generally by recrystallisation. This reaction sequence as described generates the aminocyclohexylester as the hydrochloride salt, unless an acid scavenger such as triethylamine is added to the mixture, in which case the product is the free base. The hydrochloride may be converted, if desired, to the free base form by known methodologies, and subsequently, if desired, to other acid addition salts by reaction with inorganic or organic acids. Acid addition salts can also be prepared metathetically by reacting one acid addition salt with an acid which is stronger than that of the anion of the initial salt.

40 [0053] Alternative routes based on known methodologies, such as those described below, may be used to prepare the aminocyclohexylester compounds of the present invention. The carboxylic acid may be converted to an alternative reactive derivative such as an activated ester, anhydride or acyl imidazole and reacted with the appropriate 1,2-aminocyclohexanol or 1,2-aminocyclohexanethiol. The carboxylic acid may be reacted directly with the aminoalcohol or aminothiol with the aid of a coupling reagent such as dicyclohexylcarbodiimide. The starting 1,2-aminocyclohexanol or 1,2-aminocyclohexanethiol compounds are prepared by reaction sequences well known in the art. For example, *trans*-1,2-aminocyclohexanols are commonly prepared by the ring-opening reaction of cyclohexene oxide with the appropriate amine. The starting carboxylic acids are known or are prepared by reaction sequences well known in the art.

45 [0054] The synthesis procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to those of ordinary skill in the art to perform the synthesis, isolation, and purification of the preferred compounds described herein and other analogous compounds. Individual enantiomers may be obtained, if

desired, from mixtures of the different forms by known methods of resolution, such as the formation of diastereomers, followed by recrystallisation.

[0055] The compounds of the above formulae may be in the form of a solvate or a pharmaceutically acceptable salt, e.g., an acid addition salt. Such salts include hydrochloride, sulfate, phosphate, citrate, fumarate, methanesulfonate, acetate, tartrate, maleate, lactate, mandelate, salicylate, succinate and other salts known in the art.

[0056] A compound of the present invention may be prepared as a composition by combining it with a pharmaceutically acceptable carrier or diluent. Suitable carriers or diluents include physiological saline. It will be evident to those of ordinary skill in the art that a composition of the present invention may contain more than one aminocyclohexyl ester and/or thioester compound.

[0057] As noted above, the present invention provides for utilizing the compounds described above in *in vitro* and *in vivo* methods. In one aspect, ion channels, such as cardiac sodium channels, are blocked *in vitro* or *in vivo*. A preparation that contains ion channels is contacted with, or a warm-blooded animal is administered, an effective amount of an aminocyclohexyl ester and/or thioester compound. Suitable preparations containing cardiac sodium channels include cells isolated from cardiac tissue as well as cultured cell lines. The step of contacting includes, for example, incubation of ion channels with a compound under conditions and for a time sufficient to permit blockage of the channels by the compound.

[0058] In another aspect, the compounds described above are provided for treating arrhythmia. As used herein, "treating arrhythmia" refers to both therapy for arrhythmia and for the prevention of arrhythmias occurring in a heart that is susceptible to arrhythmia. An effective amount of a composition of the present invention is used to treat arrhythmia in a warm-blooded animal, such as a human. Methods of administering effective amounts of antiarrhythmic agents are well known in the art and include the administration of an oral or parenteral dosage form. Such dosage forms include, but are not limited to, parenteral solutions, tablets, capsules, sustained release implants, and transdermal delivery systems. Generally, oral or intravenous administration is preferred. The dosage amount and frequency are selected to create an effective level of the agent without harmful effects. It will generally range from a dosage of from about 0.1 to about 100 mg/kg/day, and typically from about 0.1 to 10 mg/kg where administered orally or intravenously for antiarrhythmic effect.

[0059] Administration of compositions of the present invention may be carried out in combination with the administration of other agents. For example, it may be desired to administer an opioid antagonist, such as naloxone, if a compound exhibits opioid activity where such activity may not be desired. The naloxone may antagonize opioid activity of the administered compound without adverse interference with the antiarrhythmic activity.

[0060] In order to assess whether a compound has a desired pharmacological activity within the present invention, it is subjected to a series of tests. In the first of such tests, a compound is given as increasing (doubling with each dose) intravenous boluses every 8 minutes to a pentobarbital anesthetized rat. The effects of the compound on blood pressure, heart rate and the ECG are measured 30 seconds, 1, 2, 4 and 8 minutes after each dose. Increasing doses are given until the animal dies. The cause of death is identified as being of either respiratory or cardiac origin. This test gives an indication as to whether the compound is blocking sodium channels and/or potassium channels, and in addition gives information about acute toxicity. The indices of sodium channel blockade are increasing P-R interval and QRS widening of the ECG. Potassium channel blockade results in Q-T interval prolongation of the ECG.

[0061] A second test involves administration of a compound as an infusion to pentobarbital anesthetized rats in which the left ventricle is subjected to electrical square wave stimulation performed according to a preset protocol described in further detail below. This protocol includes the determination of thresholds for induction of extrasystoles and ventricular fibrillation. In addition, effects on electrical refractoriness are assessed by a single extra beat technique. In addition effects on blood pressure, heart rate and the ECG are recorded. In this test, sodium channel blockers produce the ECG changes expected from the first test. In addition, sodium channel blockers also raise the thresholds for induction of extrasystoles and ventricular fibrillation. Potassium channel blockade is revealed by increasing refractoriness and widening of the Q-T intervals of the ECG.

[0062] A third test involves exposing isolated rat hearts to increasing concentrations of a compound. Ventricular pressures, heart rate, conduction velocity and ECG are recorded in the isolated heart in the presence of varying concentrations of the compound. This test provides evidence for direct toxic effects on the myocardium. Additionally, selectivity, potency and efficacy of action of a compound can be ascertained under conditions simulating ischaemia. Concentrations found to be effective in this test are expected to be efficacious in the electrophysiological studies.

[0063] A fourth test is estimation of the antiarrhythmic activity of a compound against the arrhythmias induced by coronary artery occlusion in anaesthetized rats. It is expected that a good antiarrhythmic compound will have antiarrhythmic activity at doses which have minimal effects on either the ECG, blood pressure or heart rate under normal conditions.

[0064] A compound is also tested directly for effects on sodium and potassium currents in isolated rat myocytes. Isolated rat myocytes are obtained in the conventional manner from isolated hearts. They are used in voltage clamp studies. In order to obtain adequate voltage clamps for estimation of a compound's effects on sodium and potassium

currents, the whole-cell patch clamp technique is used. In this technique, a microelectrode is attached to a cell in such a manner that the cell's internal contents are in free communication with the electrode's content. Using the appropriate buffers and conventional voltage step protocols, both sodium and potassium currents can be identified. The activity of a compound is tested on these currents.

5 [0065] All of the foregoing tests are performed using rat tissue. In order to ensure that a compound is not having effects which are only specific to rat tissue, further experiments are performed in dogs and primates. In order to assess possible sodium channel and potassium channel blocking actions *in vivo* in dogs, a compound is tested for effects on the ECG, ventricular epicardial conduction velocity and responses to electrical stimulation. An anesthetized dog is subjected to an open chest procedure to expose the left ventricular epicardium. After the pericardium is removed from
10 the heart a recording/stimulation electrode is sewn onto the epicardial surface of the left ventricle. Using this array, and suitable stimulation protocols, conduction velocity across the epicardium as well as responsiveness to electrical stimulation can be assessed. This information coupled with measurements of the ECG allows one to assess whether sodium and/or potassium channel blockade occurs. As in the first test in rats, a compound is given as a series of increasing bolus doses. At the same time possible toxic effects of a compound on the dog's cardiovascular system is
15 assessed.

[0066] The effects of a compound on the ECG and responses to electrical stimulation are also assessed in intact, halothane anesthetized baboons (*Papio anubis*). In this preparation, a blood pressure cannula and ECG electrodes are suitably placed in an anesthetized baboon. In addition, a stimulating electrode is placed into the right ventricle, together with a monophasic action potential electrode. As in the tests described above, ECG and electrical stimulation
20 responses to a compound reveal the possible presence of sodium and/or potassium channel blockade. The monophasic action potential also reveals whether a compound widens the action potential, an action expected of a potassium channel blocker.

[0067] The present invention also provides compounds for use in the manufacture of a medicament for the treatment
25 of arrhythmia. Aminocyclohexyl ester and/or thioester compounds including those compounds described above may be used in the manufacture of such a medicament.

[0068] The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the above formulae. The kit also includes instructions for the use of the pharmaceutical composition for the blocking of ion channels or for the treatment of arrhythmia. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for
30 the preparation of an intravenous injection. It will be evident to those of ordinary skill in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

[0069] The following examples are offered by way of illustration and not by way of limitation.
35

EXAMPLES

EXAMPLE 1

40 (\pm)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy)acetate monohydrochloride

(Compound #1)

[0070]

45 (i) Pyrrolidine (10.5 g, 148 mmol), cyclohexene oxide (15 mL, 148 mmol) and water (5 mL) are refluxed under nitrogen until GC or tlc analysis shows the reaction to be complete. The cooled mixture is partitioned between saturated sodium hydroxide solution (150 mL) and ether (150 mL). The aqueous layer is washed with additional ether (75 mL) and the combined ether layers are dried over sodium sulfate. The ether is removed *in vacuo* to leave the crude aminoalcohol (26 g), which is vacuum distilled (bp 51°C at full vacuum) to give (\pm)-*trans*-[2-(1-pyrrolidinyl)]cyclohexanol.
50

55 (ii) 3,4-Dichlorophenoxyacetic acid (2.62 g, 12 mmol) is refluxed in thionyl chloride (10 mL) under nitrogen for 1 hour. After stirring at room temperature for a further hour, the thionyl chloride is removed *in vacuo* to leave an orange oil, which is dissolved in chloroform (10 mL). The acid chloride solution is refluxed for 12 hours with a solution of (\pm)-*trans*-[2-(1-pyrrolidinyl)]cyclohexanol (2 g, 12 mmol) in chloroform (5 mL) under nitrogen. Ether (40 mL) is added to the cooled mixture, the mixture is stirred for 30 min., and the crude product is filtered off (3.61 g) and washed with ether. It is recrystallised from the minimum volume of hot methanol/ether to yield the title com-

pound.

EXAMPLE 2

5 (\pm)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](1-naphthoxy)acetate monohydrochloride

(Compound #2)

10 [0071] The title compound is prepared according to the method described in Example 1(ii), using 1-naphthoxyacetic acid (2.4 g, 12 mmol) to prepare the acid chloride as a yellow solid, which is dissolved in chloroform (25 mL). This solution is added to a solution of (\pm)-*trans*-[2-(1-pyrrolidinyl)cyclohexanol prepared as in Example 1(i) (2 g, 12 mmol) in chloroform (5 mL) under nitrogen. The mixture is refluxed for 10 hours. All solvent is removed *in vacuo*. The resulting solid is mixed with hot ethyl acetate (100 mL) and methanol is added until it dissolves. On cooling, the solid is collected and washed with ethyl acetate, and recrystallised from hot methanol/ethyl acetate to give the title compound.

15

EXAMPLE 3

(\pm)-*trans*-{2-[N-(3-azabicyclo[3.2.2]nonyl)]cyclohexyl}(3,4-dichlorophenoxy)acetate monohydrochloride

20 (Compound #3)

[0072]

25 (i) (\pm)-*trans*-{2-[N-(3-Azabicyclo[3.2.2]nonyl)]}cyclohexanol is prepared according to the method described in Example 1(i) by refluxing 3-azabicyclo[3.2.2]nonane (5 g, 40 mmol), cyclohexene oxide (3.9 mL, 40 mmol) and water (3 mL) for 5 hours. The crude product, a waxy yellowish solid obtained on removal of ether, is used without further purification.

30 (ii) A chloroform solution (15 mL) of 3,4-dichlorophenoxyacetyl chloride, prepared from 3,4-dichlorophenoxyacetic acid (2 g, 9 mmol) as in Example 1(ii), is added to a solution of (\pm)-*trans*-{2-[N-(3-azabicyclo[3.2.2]nonyl)]}cyclohexanol (2 g, 9 mmol) in chloroform (7 mL) under nitrogen. The mixture is refluxed for 12 hours. Ether (30 mL) is added to the cooled mixture, and the crude product is filtered off and washed with ether. It is recrystallised from the minimum volume of hot ethyl acetate to yield the title compound.

35 EXAMPLE 4

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl](3,4-dichlorophenoxy)acetate monohydrochloride

40 (Compound #4)

[0073]

45 (i) (\pm)-*trans*-[2-(4-Morpholinyl)]cyclohexanol is prepared by the method detailed in Example 1(i), refluxing morpholine (5 g, 57 mmol), cyclohexene oxide (5.8 mL, 57 mmol) and water (3 mL) for 2 hours. The crude product is purified by full vacuum distillation (bp 75-80°C).

50 (ii) A chloroform solution (10 mL) of 3,4-dichlorophenoxyacetyl chloride, prepared from 3,4-dichlorophenoxyacetic acid (2.4 g, 11 mmol) as in Example 1(ii), is added to a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol (2 g, 11 mmol) in chloroform (5 mL) under nitrogen. The mixture is refluxed for 8 hours. The crude product is filtered off and washed with ether. More ether may be added to the filtrate to yield further crude product. The product is recrystallised from hot methanol to give the title compound.

EXAMPLE 5

(\pm)-*trans*-[2-(1-hexahydroazepinyl)cyclohexyl](3,4-dichlorophenoxy)acetate monohydrochloride

5 (Compound #5)

[0074]

10 (i) (\pm)-*trans*-[2-(1-Hexahydroazepinyl)]cyclohexanol is prepared by the method detailed in Example 1(i), refluxing hexamethyleneimine (17.3 mL, 0.15 mol), cyclohexene oxide (15.5 mL, 0.15 mol) and water (5 mL). The product is purified by full vacuum distillation (bp 62–65°C).

15 (ii) A chloroform solution (10 mL) of 3,4-dichlorophenoxyacetyl chloride, prepared from 3,4-dichlorophenoxyacetic acid (2.36 g, 11 mmol) as in Example 1(ii), is added to a solution of (\pm)-*trans*-[2-(1-hexahydroazepinyl)]cyclohexanol (2 g, 10 mmol) in chloroform (5 mL) under nitrogen. The mixture is refluxed for 10 hours. The crude product which precipitates on adding ether to the mixture, is filtered off and washed with ether. It is recrystallised from hot methanol (4 mL), and washed with ether, to give the title compound.

EXAMPLE 6

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(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]benzo[b]thiophene-3-acetate monohydrochloride

(Compound #6)

25 [0075] 3-Thianaphtheneacetic acid (4.81 g, 25 mmol) is refluxed in thionyl chloride (16 mL) under nitrogen for 1 hour. After stirring at room temperature for a further 20 min., the thionyl chloride is removed *in vacuo* to leave a brown oil, which is dissolved in chloroform (10 mL). The acid chloride solution is added to a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol prepared as in Example 4(i) (4.5 g, 24.3 mmol) in chloroform (5 mL) under nitrogen. The mixture is refluxed for 11 hours. Ether (25 mL) is added to the cooled mixture and the crude product is filtered off and washed with ether (3 x 10 mL). The product may be recrystallised from hot methanol/ether to give the title compound.

EXAMPLE 7

35

(\pm)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](cyclohexyl)acetate monohydrochloride

(Compound #7)

40 [0076] The title compound is prepared according to the method described in Example 1(ii), using cyclohexylacetic acid (4.4 g, 31 mmol) to prepare the acid chloride as a pale yellow oil, which is dissolved in chloroform (10 mL). This solution is added to a solution of (\pm)-*trans*-[2-(1-pyrrolidinyl)]cyclohexanol prepared as in Example 1(i) (5 g, 30 mmol) in chloroform (10 mL) under nitrogen. The mixture is refluxed for 15 hours. The solvent is removed *in vacuo* to leave a solid. The crude product may be recrystallised from hot ethyl acetate or methanol/diethyl ether to give the title compound.

45

EXAMPLE 8

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]naphthyl- 1-acetate monohydrochloride

(Compound #8)

50

[0077] 1-Naphthylacetic acid (5.30 g, 28.5 mmol) is refluxed in thionyl chloride (10 mL) under nitrogen for 1 hour. After stirring at room temperature for a further 90 min., the thionyl chloride is removed *in vacuo* to leave an orange-brown oil, which is dissolved in chloroform (10 mL). The acid chloride solution is slowly added to a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol prepared as in Example 4(i) (5.0 g, 27 mmol) in chloroform (15 mL) under nitrogen. The mixture is refluxed for 5 hours. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (150 mL) and ether (100 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 50 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (3 x 50 mL), and the combined ether extracts are washed with water until GC shows no unreacted aminoalcohol in the

ether. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The residue is dissolved in ether (40 mL) and dichloromethane (5 mL) and treated with HCl in ether to precipitate the salt. It is washed with ether and recrystallised from ethyl acetate/methanol to yield the title compound.

5 EXAMPLE 9

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]naphthyl-2-acetate monohydrochloride

(Compound #9)

10 [0078] 2-Naphthylacetyl chloride is prepared according to the method described in Example 8 using 2-naphthylacetic acid (2.64 g, 14.2 mmol) to give the corresponding acid chloride as a yellow solid which is dissolved in chloroform (10 mL). The solution is refluxed for 9 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol (2.5 g, 13.5 mmol) in chloroform (10 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is partitioned between 1M 15 sodium hydroxide solution (100 mL) and dichloromethane (80 mL). The organic layer is separated and the aqueous is washed with more dichloromethane (2 x 75 mL). The combined dichloromethane extracts are dried over sodium sulfate, and the solvent is removed to leave the crude free ester. This may be purified by column chromatography using silica gel and chloroform/ethyl acetate (3:1) as eluent. The free ester is converted to the salt by treatment with HCl in ether/dichloromethane (3:1). The resulting solid is washed with ether and recrystallised from hot methanol to yield the title 20 compound.

EXAMPLE 10

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]phenylacetate monohydrochloride

25 (Compound #10)

30 [0079] Phenylacetyl chloride is prepared according to the method described in Example 8 using phenylacetic acid (2.13 g, 15.6 mmol) to give a pale yellow oil which is dissolved in chloroform (10 mL). This solution is refluxed for 12 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol (2.75 g, 14.9 mmol) in chloroform (10 mL) under nitrogen. The reaction mixture is partitioned between 1M sodium hydroxide solution (100 mL) and dichloromethane (80 mL). The organic layer is separated and the aqueous is washed with more dichloromethane (2 x 50 mL). The combined dichloromethane extracts are dried over sodium sulfate, and the solvent is removed to leave the crude free ester. This is purified by column chromatography and converted to the hydrochloride salt as described in Example 9. 35 The product is recrystallised from hot methanol to yield the title compound.

EXAMPLE 11

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl](3,4-dichlorophenyl)acetate monohydrochloride

40 (Compound #11)

45 [0080] 3,4-Dichlorophenylacetyl chloride is prepared according to the method described in Example 8, using 3,4-dichlorophenylacetic acid (2.62 g, 12.8 mmol) to give a yellow oil which is dissolved in chloroform (15 mL). This solution is refluxed for 9 hours with a solution of (1)-*trans*-[2-(4-morpholinyl)]cyclohexanol (2.25 g, 12.2 mmol) in chloroform (10 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (75 mL) and ether (75 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 30 mL), and then basified to pH14 by the addition of 50% sodium hydroxide solution. This is then extracted with ether (4 x 30 mL), and the combined ether extracts are washed with water until GC shows no unreacted aminoalcohol in the ether. 50 The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The residue is dissolved in ether (20 mL) and treated with HCl in ether to precipitate the salt. It is washed with ether and recrystallised from hot methanol to yield the title compound.

EXAMPLE 12

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl](4-nitrophenyl)acetate monohydrochloride

5 (Compound #12)

[0081] 4-Nitrophenylacetyl chloride, prepared according to the method described in Example 8 using 4-nitrophenylacetic acid (5.4 g, 29.8 mmol), is dissolved in chloroform (15 mL). This solution is refluxed for 9 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)cyclohexanol (5.25 g, 28.3 mmol) in chloroform (15 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (60 mL) and ether (50 mL). The ether layer is separated and the aqueous layer is washed with more ether (2 x 50 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (5 x 60 mL), and the combined ether extracts are washed repeatedly with water to remove any unreacted aminoalcohol. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The residue is dissolved in ether (20 mL) and treated with HCl in ether to precipitate the salt. It is washed with ether and recrystallised from hot methanol to yield the title compound.

EXAMPLE 13

20 (\pm)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexyl]naphthyl-2-acetate dihydrochloride

(Compound #13)

[0082]

25 (i) (\pm)-*trans*-[2-(4-Methyl-1-piperazinyl)cyclohexanol is prepared by the method detailed in Example 1(i), refluxing 1-methylpiperazine (16.6 mL, 150 mmol), cyclohexene oxide (15.2 mL, 150 mmol) and water (5 mL) for 5 hours. The crude product is purified by full vacuum distillation (bp 94°C) to give a white solid.

30 (ii) 2-Naphthylacetyl chloride is prepared according to the method described in Example 8 using 2-naphthylacetic acid (2.47 g, 13.3 mmol) to give a yellow solid which is dissolved in chloroform (15 mL). This solution is added to a solution of (\pm)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexanol (2.5 g, 12.6 mmol) in chloroform (10 mL), and the mixture is refluxed for 11 hours under nitrogen. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (100 mL) and ether (60 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 30 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (4 x 30 mL), and the combined ether extracts are washed repeatedly with water to remove any unreacted aminoalcohol. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The free ester is dissolved in ether/dichloromethane (35 mL, 4:3) and converted to the dihydrochloride salt by treatment with an excess of HCl in the same solvent. The resulting solid is washed with ether and recrystallised from hot methanol to yield the title compound.

EXAMPLE 14

(\pm)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexyl]naphthyl-1-acetate monohydrochloride

45 (Compound #14)

[0083] 1-Naphthylacetyl chloride is prepared according to the method described in Example 8 using 1-naphthylacetic acid (2.47 g, 13.3 mmol) to give a yellow oil which is dissolved in chloroform (10 mL). This solution is added to a solution of (\pm)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexanol (2.5 g, 12.6 mmol) in chloroform (10 mL), and the mixture is refluxed for 11 hours under nitrogen. The crude free ester is isolated as described in Example 13, and is converted to the monohydrochloride salt in ether/dichloromethane (35 mL, 6:1) by treatment with 1 equivalent of HCl in the same solvent. The resulting solid is washed with ether and recrystallised from hot ethyl acetate/methanol to yield the title compound.

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EXAMPLE 15

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]-1-naphthoate monohydrochloride

5 (Compound #15)

[0084] 1-Naphthoyl chloride, prepared according to the method described in Example 8 using 1-naphthoic acid (2.44 g, 14.2 mmol), is dissolved in chloroform (15 mL). This solution is refluxed for 60 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)cyclohexanol (2.5 g, 13.5 mmol) in chloroform (12 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is treated as in Example 13 to give the crude free ester. This is purified by column chromatography using silica gel and chloroform/ethyl acetate (9:1) as eluent. The free ester is converted to the salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot ethyl acetate/methanol to yield the title compound.

15 EXAMPLE 16

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]benzo[b]thiophene-4-acetate monohydrochloride

20 (Compound #16)

[0085] 4-Thianaphtheneacetyl chloride is prepared according to the method described in Example 8 using 4-thianaphtheneacetic acid (2.44 g, 12.8 mmol) to give a redbrown oil which is dissolved in chloroform (15 mL). This solution is refluxed for 27 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)cyclohexanol (2.27 g, 13.5 mmol) in chloroform (10 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is treated as in Example 13 to give the crude free ester. This is purified by column chromatography using silica gel and chloroform/ethyl acetate (9:1) as eluent. The free ester is converted to the salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot methanol to yield the title compound.

30 EXAMPLE 17

(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl](4-bromophenyl)acetate monohydrochloride

35 (Compound #17)

[0086] 4-Bromophenylacetyl chloride is prepared according to the method described in Example 8 using 4-bromophenylacetic acid (2.75 g, 12.8 mmol) to give an oil which is dissolved in chloroform (10 mL). This solution is refluxed for 19 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)cyclohexanol (2.25 g, 12.2 mmol) in chloroform (10 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is treated as in Example 13 to give the crude free ester, which is then dissolved in 1M hydrochloric acid (70 mL). Sodium chloride (14 g) is added to the solution which is then extracted with chloroform (60 mL then 2 x 40 mL). The combined extracts are dried over sodium sulfate and the solvent removed *in vacuo*. The residue is recrystallised from hot ethyl acetate/methanol to give the title compound.

EXAMPLE 18

45 (\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]-3,4-dichlorocinnamate monohydrochloride

(Compound #18)

[0087] 3,4-Dichlorocinnamyl chloride is prepared according to the method described in Example 8 using 3,4-dichlorocinnamic acid (2.46 g, 11.4 mmol) to give an oil which is dissolved in chloroform (10 mL). This solution is refluxed for 35 hours with a solution of (\pm)-*trans*-[2-(4-morpholinyl)cyclohexanol (2.0 g, 10.8 mmol) in chloroform (10 mL) under nitrogen. The solvent is removed *in vacuo* and the residue partitioned between 10% aqueous sodium hydroxide (50 mL) and dichloromethane (50 mL). The aqueous layer is extracted with more dichloromethane (2 x 50 mL) and the combined extracts are dried over sodium sulfate. The solvent is removed and the crude ester is purified by column chromatography using silica gel and chloroform/ethyl acetate (1:1) as eluent. The free ester is converted to the salt by treatment with HCl in dichloromethane/ether (1:4). The resulting solid is washed with ether and recrystallised from hot methanol to yield the title compound.

EXAMPLE 19

(\pm)-*trans*-[2-(1-piperidinyl)cyclohexyl]thiophenoxyacetate monohydrochloride

5 (Compound #19)

[0088]

10 (i) (\pm)-*trans*-[2-(1-Piperidinyl)]cyclohexanol is prepared by the method detailed in Example 1(i), refluxing piperidine (14.8 mL, 0.15 mol), cyclohexene oxide (15.5 mL, 0.15 mol) and water (5 mL). The product is purified by full vacuum distillation to give a colorless liquid.

15 (ii) A chloroform (10 mL) solution of thiophenoxyacetyl chloride, prepared from thiophenoxyacetic acid (1.85 g, 11 mmol) as in Example 8, is refluxed for 12 hours with a solution of (1)-*trans*-[2-(1-piperidinyl)]cyclohexanol (1.85 g, 10 mmol) in chloroform (15 mL) under nitrogen. The crude product, which precipitates on cooling the mixture, is filtered off and washed with ether. It is recrystallised from hot methanol (4 mL), and washed with ether, to give the title compound.

EXAMPLE 20

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(\pm)-*trans*-[2-(4-morpholinyl)cyclohexyl]-2-(1-naphthyl)propionate monohydrochloride

(Compound #20)

25 [0089]

30 (i) 1-Naphthylacetic acid (10 g, 53.7 mmol) is dissolved in dry THF (150 mL) under nitrogen. The solution is cooled to -10°C, treated with 1.6M butyl lithium in hexanes (72 mL, 115 mmol), and stirred for 15 minutes. A solution of iodomethane (3.7 mL, 59.4 mmol) in dry THF (50 mL) is added, and the mixture is allowed to warm to room temperature and stir for several hours. The solvent is removed *in vacuo*, and the residue dissolved in 5% sodium hydroxide solution (500 mL), washed with ether (3 x 200 mL), and then acidified by the addition of 6N hydrochloric acid. The aqueous is then extracted with dichloromethane (3 x 200 mL), the organic extracts are dried over sodium sulfate, and the solvent removed to leave 2-(1-naphthyl)propionic acid as a white solid.

35 (ii) 2-(1-Naphthyl)propionyl chloride, prepared according to the method described in Example 8 using 2-(1-naphthyl) propionic acid (2.55 g, 12.8 mmol), is dissolved in chloroform (10 mL). The acid chloride solution is added to a solution of (\pm)-*trans*-[2-(4-morpholinyl)]cyclohexanol prepared as in Example 4(i) (2.25 g, 12.2 mmol) in chloroform (10 mL) under nitrogen. The mixture is refluxed for 14 hours. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (150 mL) and ether (100 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 50 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (3 x 50 mL), and the combined ether extracts are washed with water until GC shows no unreacted aminoalcohol in the ether. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The residue is dissolved in ether (40 mL) and dichloromethane (5 mL) and treated with HCl in ether to precipitate the salt. It is washed with ether and recrystallised from ethyl acetate/methanol to yield the title compound.

EXAMPLE 21

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(\pm)-(1 α ,2 β ,4 β ,5 β)-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzofuran-2-acetate monohydrochloride

(Compound #21)

[0090]

55 (i) Iodine (122 g, 480 mmol) is added gradually over 5 hours to a mixture of 1,4-cyclohexadiene (77 g, 963 mmol) and sodium iodate (51.5 g, 240 mmol) in glacial acetic acid (50 mL). This mixture is stirred for a further 1 hour and then water (17.3 g, 963 mmol) and potassium acetate (94.3 g, 963 mmol) are added and the mixture is refluxed for 3 hours. The acetic acid is removed by vacuum distillation, and the residue is dissolved in ether (400 mL) and

washed with saturated sodium metabisulfite solution (400 mL). The aqueous layer is extracted with ethyl acetate (3 x 80 mL), and the combined organic extracts are dried over sodium sulfate and the solvent removed. The resulting oil is dissolved in ether (200 mL) and treated with 10% potassium hydroxide in methanol until chromatography shows the conversion to *cis*-4,5-cyclohexenediol to be complete. The mixture is neutralized by the addition of solid carbon dioxide. The solvent is removed and the product is partitioned between saturated sodium chloride solution and ethyl acetate. The ethyl acetate extracts are dried over sodium sulfate, the solvent is removed and the product, *cis*-4,5-cyclohexenediol, is purified by vacuum distillation (bp 90-100°C at full vacuum) to give a white solid.

- (ii) A solution of the diol (37.1 g, 325 mmol) in dry THF (600 mL) is added over 1 hour to a cooled, stirred suspension of sodium hydride (32 g of a 60% dispersion in mineral oil, 800 mmol) in dry THF (800 mL) under nitrogen. A solution of methyl iodide (60 mL, 964 mmol) in THF (60 mL) is added and the mixture stirred for 12 hours. The reaction is quenched by the addition of moist ether followed by water. The solvent is removed and the residue partitioned between water (200 mL) and ether (300 mL). The aqueous layer is extracted with additional ether (2 x 75 mL) and the combined organic extracts are dried over sodium sulfate and the solvent removed. The product, 4,5-dimethoxycyclohexene, is purified by vacuum distillation (bp 90°C at 20 mmHg) to give a colorless oil.
- (iii) m-Chloroperbenzoic acid (43 g, 250 mmol) is dissolved in ether (400 mL), any aqueous layer is separated, and the ether solution is dried over sodium sulfate and added quickly dropwise to a solution of 4,5-dimethoxycyclohexene (17.7 g, 125 mmol) in ether (250 mL). The mixture is stirred for 12 hours, most of the ether is removed (450 mL) *in vacuo*, and dichloromethane is added (400 mL). The solution is washed with 20% sodium metabisulfite solution (3 x 200 mL), saturated sodium bicarbonate solution (3 x 200 mL) and brine (3 x 200 mL). The solvent is removed and the epoxide is refluxed with pyrrolidine (40 mL, 480 mmol) and water (10 mL) for 2 hours. After cooling, 25% sodium hydroxide solution (30 mL) is added and the excess pyrrolidine removed by distillation. The product, 4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexanol, is extracted into dichloromethane (3 x 100 mL) and purified by distillation (bp 90-100°C at full vacuum).
- (iv) Benzofuran-2-acetyl chloride, prepared according to the method described in Example 8 using benzofuran-2-acetic acid (2.1 g, 12 mmol), is dissolved in chloroform (15 mL). This solution is added to a solution of 4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexanol (2.5 g, 11 mmol) in chloroform (10 mL), and the mixture is refluxed for 11 hours under nitrogen. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (100 mL) and ether (60 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 30 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (4 x 30 mL), and the - combined ether extracts are washed repeatedly with water to remove any unreacted aminoalcohol. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The free ester is converted to the hydrochloride salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot methanol to yield the title compound.

EXAMPLE 22

(\pm)-*trans*-(2-[bis(2-methoxyethyl)amino]cyclohexyl)fluorene-9-carboxylate monohydrochloride

(Compound #22)

[0091]

- (i) The intermediate aminoalcohol, (\pm)-*trans*-(2-[bis(2-methoxyethyl)amino]cyclohexanol, is prepared by the method detailed in Example 1 (i), refluxing bis(2-methoxyethyl)amine (25 mL, 169 mol), cyclohexene oxide (17.2 mL, 170 mmol) and water (8 mL) for 30 hours. The crude product is purified by full vacuum distillation (bp 83-85°C) to give a clear liquid.
- (ii) 9-Fluorenecarboxylic acid (2.43 g, 11.5 mmol) is converted to the corresponding acid chloride according to the method described in Example 8. The resulting white solid is dissolved in chloroform (10 mL) and refluxed under nitrogen with a chloroform solution (10 mL) of (\pm)-*trans*-(2-[bis(2-methoxyethyl)amino]cyclohexanol (2.7 g, 11 mmol) for 20 hours. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (100 mL) and ether (100 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 50 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (4 x 40 mL), and the combined ether extracts are washed repeatedly with water to remove any unreacted aminoalcohol.

The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The free ester is converted to the hydrochloride salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot methanol to yield the title compound.

5 EXAMPLE 23

S- $\{(\pm)$ -*trans*-[2-(4-morpholinyl)cyclohexyl]](3,4-dimethoxyphenyl)thioacetate monohydrochloride

(Compound #23)

10

[0092]

(i) Morpholine (7.6 g, 87 mmol), cyclohexene sulfide (10 g, 88 mmol) and water (5 mL) are refluxed under nitrogen for 5 hours or until GC or tlc analysis show the reaction to be complete. The cooled mixture is partitioned between saturated sodium hydroxide solution (150 mL) and dichloromethane (150 mL). The aqueous layer is washed with dichloromethane (2 x 50 mL) and the combined organic layers are dried over sodium sulfate. The solvent is removed *in vacuo* to give (\pm) -*trans*-[2-(4-morpholinyl)cyclohexanethiol which is purified by full vacuum distillation (bp 90-100°C).

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(ii) (3,4-dimethoxyphenyl)acetyl chloride is prepared according to the method described in Example 8 using 3,4-dimethoxyphenylacetic acid (2.85 g, 14.5 mmol) to give a brown oil which is dissolved in chloroform (10 mL). This solution is refluxed for 3 hours with a solution of (\pm) -*trans*-[2-(4-morpholinyl)cyclohexanethiol (2.8 g, 14 mmol) in chloroform (10 mL) under nitrogen. The reaction mixture is partitioned between 1M sodium hydroxide solution (100 mL) and dichloromethane (80 mL). The organic layer is separated and the aqueous is washed with more dichloromethane (2 x 50 mL). The combined dichloromethane extracts are dried over sodium sulfate, and the solvent is removed to leave the crude free ester. This is purified by column chromatography and converted to the hydrochloride salt by treatment with HCl in ether. The product is recrystallised from hot ethyl acetate/methanol to yield the title compound.

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[0093] Compounds prepared according to the methods described above were generally characterized by proton and/or carbon-13 NMR and/or infrared spectroscopy. Elemental analysis was obtained for compounds listed in Table 1.

EXAMPLE 24

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S- $\{(\pm)$ -*trans*-[2-(4-morpholinyl)cyclohexyl]]naphthyl-1-thioacetate monohydrochloride

(Compound #24)

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[0094] 1-Naphthylacetyl chloride is prepared according to the method described in Example 8 using 1-naphthylacetic acid (2.0 g, 10.8 mmol) to give a yellow oil which is dissolved in chloroform (10 mL). This solution is added to a solution of (\pm) -*trans*-[2-(4-morpholinyl)cyclohexanethiol (2 g, 10 mmol) in chloroform (10mL), and the mixture is stirred at room temperature for 8 hours under nitrogen. The solvent is removed and the residue is partitioned between 1M hydrochloric acid (100 mL) and ether (80 mL). The organic layer is separated and the aqueous is washed with more ether (2 x 60 mL). The aqueous mixture is basified to pH>12 by the addition of 50% sodium hydroxide solution, and extracted with ether (1 x 80 mL, 2 x 50 mL). These ether extracts of the basic aqueous solution are washed repeatedly with water to remove any unreacted aminothiol, dried over sodium sulfate, and the solvent is removed to leave the crude free thioester. This is converted to the hydrochloride salt by dissolving it in 1M hydrochloric acid (60 mL), adding sodium chloride (12 g), and extracting with chloroform (3 x 75 mL). The chloroform is removed *in vacuo* and the residue is recrystallised from ethyl acetate/methanol to yield the title compound.

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EXAMPLE 25

S- $\{(\pm)\text{-}trans\text{-}\{2\text{-[bis(2-methoxyethyl)amino]cyclohexyl}\}\text{-}4\text{-bromothiobenzoate monohydrochloride}$

5 (Compound #25)

[0095]

- 10 (i) The intermediate aminothiol, $(\pm)\text{-}trans\text{-}\{2\text{-[bis(2-methoxyethyl)amino]cyclohexanethiol}$, is prepared by the method detailed in Example 23(i), refluxing bis(2-methoxyethyl)amine (13 mL, 88 mmol), cyclohexene sulfide (10 g, 88 mmol) and water (8 mL).
- 15 (ii) 4-Bromobenzoyl chloride (2.4 g, 11 mmol) in chloroform (10 mL) is added to a solution of $(\pm)\text{-}trans\text{-}\{2\text{-[bis(2-methoxyethyl)amino]cyclohexanethiol}$ (2 g, 10 mmol) in chloroform (10 mL), and the mixture is stirred at room temperature for 8 hours under nitrogen. The crude free thioester is obtained using the work-up procedure described in Example 24, and is converted to the hydrochloride salt by dissolving it in 1M hydrochloric acid (60 mL), adding sodium chloride (12 g), and extracting with chloroform (3 x 75 mL). The chloroform is removed *in vacuo* and the residue is recrystallised from ethyl acetate/methanol to yield the title compound.

20 EXAMPLE 26

$(\pm)\text{-}trans\text{-}\{2\text{-[diisopropylamino]cyclohexyl}\}\text{acenaphthene-1-carboxylate monohydrochloride}$

25 (Compound #26)

[0096]

- 30 (i) The intermediate aminoalcohol, $(\pm)\text{-}trans\text{-}\{2\text{-diisopropylamino)cyclohexanol}$, is prepared by the method detailed in Example 1(i), refluxing diisopropylamine (22.3 mL, 170 mmol), cyclohexene oxide (17.2 mL, 170 mmol) and water (8 mL) for 30 hours. The crude product is purified by full vacuum distillation.
- 35 (ii) Acenaphthene-1-carboxylic acid (2.28 g, 11.5 mmol) is prepared according to the method described by P.R. Haipenny et al. in *Synthesis*, 1990, 517-519 or in U.S. Patent Nos. 4,906,655 and 5,019,588. It is converted to the corresponding acid chloride according to the method described in Example 8, and is dissolved in chloroform (10 mL) and refluxed under nitrogen with a solution of $(\pm)\text{-}trans\text{-}\{2\text{-diisopropylamino)cyclohexanol}$ (2.2 g, 11 mmol) for 20 hours. The solvent is removed *in vacuo*, and the residue is partitioned between 1M hydrochloric acid (100 mL) and ether (100 mL). The ether layer is separated and the aqueous is washed with more ether (2 x 50 mL), and then basified by the addition of 50% sodium hydroxide solution. This is then extracted with ether (4 x 40 mL), and the combined ether extracts are washed repeatedly with water to remove any unreacted aminoalcohol. The ether containing the product is then dried over sodium sulfate, and the solvent is removed to leave the crude free ester. The free ester is converted to the hydrochloride salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot acetate/methanol to yield the title compound.

40 EXAMPLE 27

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$(\pm)\text{-}trans\text{-}\{2\text{-[4-morpholinyl]cyclohexyl}\}\text{diphenylacetate monohydrochloride}$

(Compound #27)

- 50 [0097] A solution of diphenylacetylchloride (2.95 g, 128 mmol) in chloroform (10 mL) is slowly added to a solution of $(\pm)\text{-}trans\text{-}\{2\text{-[4-morpholinyl]cyclohexanol}$ prepared as in Example 4 (i) (2.25 g, 12.2 mmol) in chloroform (10 mL) under nitrogen. The mixture is refluxed for 14 hours, and the crude ester is obtained using the work-up procedure described in Example 26. It is dissolved in ether (40 mL) and dichloromethane (5 mL) and treated with HCl in ether to precipitate the salt, which is washed with ether and recrystallised from ethyl acetate/methanol to yield the title compound.

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EXAMPLE 28

(\pm)-trans-[2-(4-morpholinyl)cyclohexyl]-3-trifluoromethylbenzoate monohydrochloride

5 (Compound #28)

[0098] 3-(Trifluoromethyl)benzoylchloride (2.96 g, 14.2 mmol), is dissolved in chloroform (15 mL) and is refluxed for 60 hours with a solution of (\pm)-trans-[2-(4-morpholinyl)cyclohexanol (2.5 g, 13.5 mmol) in chloroform (12 mL) under nitrogen. The solvent is removed *in vacuo*, and the residue is treated as in Example 26 to give the crude free ester. 10 This is purified by column chromatography using silica gel and chloroform/ethyl acetate (9:1) as eluent. The free ester is converted to the salt by treatment with HCl in ether. The resulting solid is washed with ether and recrystallised from hot ethyl acetate/methanol to yield the title compound.

EXAMPLE 29

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[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]naphthal-1-acetate monohydrochloride

16

(Compound #29)

20 [0099]

(i) 7-(Pyrrolidinyl)-1-oxaspiro[4.5]decan-8-ol is prepared by the method described in Example I(i), refluxing the corresponding epoxide (5 g, 32 mmol, prepared according to the method described in U.S. Patent No. 4,737,493) with pyrrolidine (2.28 g, 32 mmol) and water (5 mL) under nitrogen until GC or tlc analysis show the reaction to be complete. The produce is purified by full vacuum distillation.

(ii) The title compound is prepared according to the method described in Example 8 using 1-naphthylacetic acid (2 g, 10.8 mmol) and 7-(pyrrolidinyl)-1-oxaspiro[4.5]decan-8-ol (2.25 g, 10 mmol). The solvent is removed *in vacuo*, and the residue is treated as in Example 8 to leave the crude free ester. This is dissolved in ether (40 mL) and dichloromethane (5 mL) and treated with HCl in ether to precipitate the salt. It is washed with ether and recrystallised from ethyl acetate/methanol to yield the title compound.

Table 1

35	Compound	Formula	Calculated	Found
	#1	C ₁₈ H ₂₄ NO ₃ Cl ₃	C 52.89, H 5.92, N 3.43%	C 52.59, H 5.78, N 3.37%
	#3	C ₂₂ H ₃₀ NO ₃ Cl ₃	C 57.09, H 6.53, N 3.03%	C 57.05, H 6.31, N 3.08%
	#4	C ₁₈ H ₂₄ NO ₄ Cl ₃	C 50.90, H 5.70, N 3.30%	C 50.88, H 5.70, N 3.25%
40	#5	C ₂₀ H ₂₈ NO ₃ Cl ₃	C 54.99, H 6.46, N 3.21%	C 54.31, H 6.49, N 3.26%
	#6	C ₂₀ H ₂₆ NO ₃ CIS	C 60.67, H 6.62, N 3.54%	C 60.69, H 6.57, N 3.58%
	#7	C ₁₈ H ₃₂ NO ₂ Cl	C 65.53, H 9.78, N 4.25%	C 65.78, H 9.84, N 4.42%
	#8	C ₂₂ H ₂₈ NO ₃ Cl	C 67.77, H 7.24, N 3.59%	C 67.47, H 7.21, N 3.57%
45	#9	C ₂₂ H ₂₈ NO ₃ Cl	C 67.77, H 7.24, N 3.59%	C 67.60, H 7.25, N 3.66%
	#10	C ₁₈ H ₂₆ NO ₃ Cl	C 63.61, H 7.71, N 4.12%	C 63.50, H 7.56, N 4.17%
	#11	C ₁₈ H ₂₄ NO ₃ Cl ₃	C 52.89, H 5.92, N 3.43%	C 52.75, H 5.90, N 3.40%
	#12	C ₁₈ H ₂₅ N ₂ O ₅ Cl	C 56.18, H 6.55, N 7.28%	C 55.85, H 6.48, N 7.20%
50	#13	C ₂₃ H ₃₂ N ₂ O ₂ Cl ₂	C 62.87, H 7.34, N 6.38%	C 62.65, H 7.22, N 6.28%
	#14	C ₂₃ H ₃₁ N ₂ O ₂ Cl	C 68.56, H 7.75, N 6.95%	C 67.63, H 7.52, N 6.91%
	#15	C ₂₁ H ₂₆ NO ₃ Cl	C 67.10, H 6.97, N 3.73%	C 67.17, H 6.90, N 3.78%
	#16	C ₂₀ H ₂₆ NO ₃ CIS	C 60.67, H 6.62, N 3.54%	C 60.40, H 6.53, N 3.51%
	#17	C ₁₈ H ₂₅ NO ₃ ClBr	C 51.63, H 6.02, N 3.34%	C 51.56, H 6.01, N 3.34%
55	#18	C ₁₉ H ₂₄ NO ₃ Cl ₃	C 54.24, H 5.75, N 3.33%	C 54.33, H 5.78, N 3.32%

EXAMPLE 30

Assessment of Antiarrhythmic Efficacy

5 [0100] Antiarrhythmic efficacy was assessed by investigating the effect of a compound on the incidence of cardiac arrhythmias in conscious rats subject to coronary artery occlusion. Rats weighing 200-300 gms were subjected to preparative surgery and assigned to groups in a random block design. In each case, the animal was anesthetized with halothane during surgical preparation. The left femoral artery was cannulated for measurement of mean arterial blood pressure and withdrawal of blood samples. The left femoral vein was also cannulated for injection of drugs. The thoracic
 10 cavity was opened and a polyethylene occluder loosely placed around the left anterior descending coronary artery. The thoracic cavity was then closed. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All cannulae and electrode leads were exteriorized in the mid scapular region. In random and double-blind manner, about 0.5 to 2 hours post-surgery, an infusion of vehicle, or the compound to be tested was given. After 15 minutes infusion, the occluder was pulled so as to produce coronary artery occlusion. ECG, arrhythmias, blood pres-
 15 sure, heart rate and mortality were monitored for 30 minutes after occlusion. Arrhythmias were recorded as ventricular tachycardia (VT) and ventricular fibrillation (VF) and scored according to Curtis, M.J. and Walker, M.J.A., *Cardiovasc. Res.* 22:656 (1988) (see Table 2).

Table 2

Score	Description
0	0-49 VPBs
1	50-499 VPBs
2	> 499 VPBs and/or 1 episode of spontaneously reverting VT or VF
3	> 1 episode of VT or VF or both (<60s total combined duration)
4	VT or VF or both (60-119s total combined duration)
5	VT or VF or both (> 119s total combined duration)
6	fatal VF starting at > 15 min after occlusion
7	fatal VF starting at between 4 min and 14 min 59s after occlusion
8	fatal VF starting at between 1 min and 3 min 59s after occlusion
9	fatal VF starting < 1 min after occlusion

Where:

VPB = ventricular premature beats

VT = ventricular tachycardia

VF = ventricular fibrillation

40 [0101] Rats were excluded from the study if they did not exhibit pre-occlusion serum potassium concentrations within the range of 2.9-3.9 mM. Occlusion is associated with increases in R-wave height and "S-T" segment elevation; and an occluded zone (measured after death by cardiogreen dye perfusion) in the range of 25%-50% of total left-ventricular weight.

45 [0102] Table 3 describes the result of tests of the compounds described therein as values of arrhythmia score at a given dose in micromoles/kg/min.

Table 3

Compound	Dose	AS
Vehicle		7
#2	20	4
#4	5	3.6
#5	4	3
#6	5	1.8
#8	2	3
#9	4	1.3
#10	10	2.2

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Table 3 (continued)

Compound	Dose	AS
#12	8	3
#15	12	2
#16	8	0.3

EXAMPLE 31

10 **Measurement of ECG Parameters**

15 [0103] Rats weighing 200-250 gms were used in this example. Animals were anesthetized with 60 mg/kg pentobarbitone i.p. The carotid artery and jugular vein were cannulated for measurement of blood pressure and drug injection, respectively. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All compounds were given as bolus injections.

20 [0104] Various ECG parameters were measured. The most sensitive of these for measuring sodium channel blockade is RSh (*J. Pharmacology Methods* 27:51-58 (1992)). Table 4 describes the results of the tests as ED₂₅ (micromoles/kg) which are the doses required to produce a 25% increase in the parameter measured (ne = not estimated). The increases in P-R interval, QRS interval and RSh indicate cardiac sodium channel blockade while the increase in Q-T interval indicates ancillary cardiac potassium channel blockade which is the property of a type 1a antiarrhythmic.

Table 4

Compound	RSh	PR	QRS	QT
#1	10	17	ne	78
#2	11	23	ne	53
#3	140	140	130	160
#4	10	44	ne	ne
#5	36	43	66	45
#6	100	ne	ne	79
#7	6	84	ne	41
#8	11	20	42	57
#9	13	ne	ne	20
#10	16	ne	ne	25
#12	17	64	82	44
#15	80	340	90	ne
#16	23	230	690	33

40 **EXAMPLE 32**

Assessment of Sodium Channel Blockade

45 [0105] Rats were prepared according to the preceding procedure. Two silver stimulating electrodes were inserted through the chest wall and implanted in the left ventricle. Square wave stimulation was used to determine threshold current for capture, ventricular fibrillation threshold current, and effective refractory period (Howard, P.G. and Walker, M.J.A., *Proc. West. Pharmacol. Soc.* 33:123-127 (1990)). Table 5 contains ED₂₅ values for these indices of cardiac sodium channel blockade, where the ED₂₅ is the infusion rate in micromoles/kg/minute of compound required to elicit a 25% increase from control. The increases in refractoriness indicate ancillary blockade of potassium channels. The threshold current for capture is represented by "iT". The fibrillation threshold current is represented by "VFT". The effective refracting period is represented by "ERP".

Table 5

Compound	iT	VFT	ERP
#1	6	3	4
#2	5	2	3

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Table 5 (continued)

Compound	iT	VFT	ERP
#5	5	4	4
#6	12	9	7
#8	5	2	4
#9	34	7	8
#10	15	11	8
#12	4	5	6
#15	33	18	20
#16	15	2	5

EXAMPLE 33

Voltage Clamp Tests

[0106] In order to directly measure cardiac sodium channel blockade, standard whole cell voltage clamp tests were carried out using single isolated adult rat cardiac cells. Results in the form of EC₅₀ values, which are micromolar concentrations required to produce a 50% reduction in sodium current, are presented in Table 6.

Table 6

Compound	
#1	200
#2	50
#3	>150
#4	>500
#6	150
#8	80
#9	>100
#10	>300
#12	>300
#15	ne
#16	225

EXAMPLE 34

Nerve Conduction Blockade

[0107] In order to establish the potency of the compounds to block nerve conduction, two *in vitro* assays were used. The first was the phrenic nerve diaphragm of the rat. The second was the hypogastric nerve vas deferens. Nerve blockade in these preparations is indicative of local anesthetic activity. Compounds were administered to the bath solution in increasing concentrations while the preparations were being stimulated with regular electrical impulses. Table 7 shows the micromolar concentrations at which the twitch response from electrical stimulation is reduced to 50% of control value.

Table 7

	Compound				
	#1	#2	#3	#5	#6
Phrenic nerve diaphragm	90	120	200	180	30
Hypogastric nerve vas deferens	40	25	300	100	100

EXAMPLE 35

Opioid-like Effects

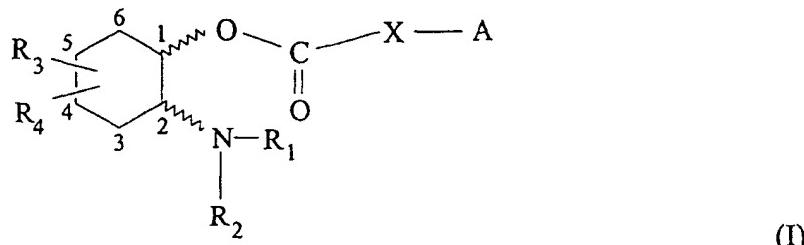
- 5 [0108] During *in vivo* tests of compound #6, it was observed that this compound induced opioid-like effects on the central nervous system of the rat. These effects were completely blocked by naloxone, an inhibitor of mu, delta and kappa opioid agonists. This provides evidence that some of the compounds may have analgesic activity through activation of opioid receptors. Examination of members of this series of compounds by analgesic assays and binding studies show the presence of opioid binding and activity.
- 10 [0109] From the foregoing, it will be evident that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

15 Claims

1. An enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

20

25



30

wherein X is a direct bond;

- 35 or $-(CH_2)_n-Y-$, where $n = 1, 2$, or 3 , and Y is a direct bond, O or S; or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S; or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

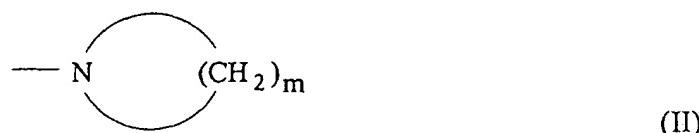
40

R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

45

or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring denoted by formula II:

50



where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of

55

one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only

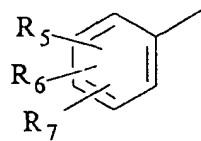
carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

5 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

10 R₃ and R₄ are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

15 A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII:

15



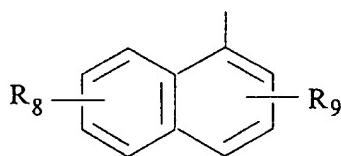
(III)

25

where R₅, R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl, and when X is a direct bond at least one of R₅, R₆ and R₇ is a hydroxy, fluorine, chlorine, bromine, trifluoromethyl, alkyl of from one to six carbon atoms, or aryl substituent, and when X is -CH=CH-, and R₁ and R₂ when taken together with the nitrogen atom to which they are attached, form a N-phenylpiperazine ring, and R₃ and R₄ are hydrogen, at least one of R₅, R₆ and R₇ is a substituent other than hydrogen;

30

35



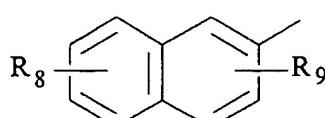
(IV)

40

where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

45

50

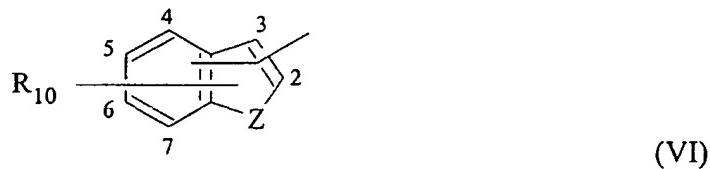


(V)

where R₈ and R₉ are defined as above;

55

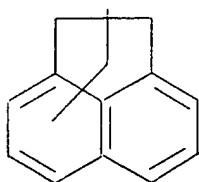
5



10

where R_{10} is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH_2 , O, S, or $N-R_{11}$ where R_{11} is hydrogen or alkyl of one to six carbon atoms;

15

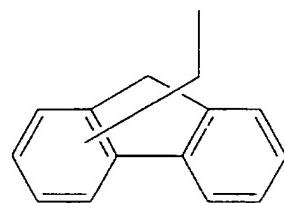


20

(VII)

only when X is a direct bond;

25



30

(VIII)

35

only when X is a direct bond;

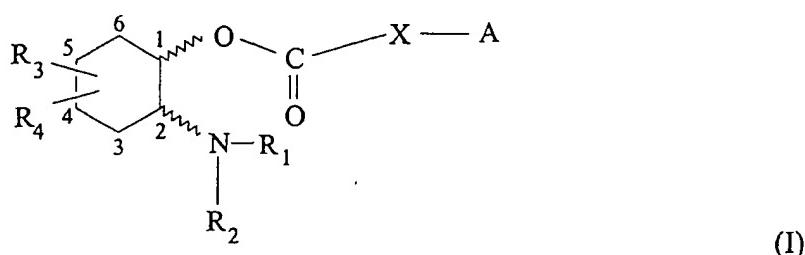
40

with the proviso that, when X is $-(CH_2)_n-Y-$, and $n = 1$, and Y is a direct bond, and R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R_3 and R_4 are hydrogen, A may not be 4-thianaphthenyl.

45

2. An enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

50



55

wherein X is a direct bond;

or $-(CH_2)_n-Y-$, where $n = 1$ and Y is a direct bond, O or S;
 or $-CH(R_{12})-$, where R_{12} is alkyl of from one to six carbon atoms;
 or $-C(R_{13})=CH-$, where R_{13} is hydrogen;

5 R_1 and R_2 are defined as in claim 1;

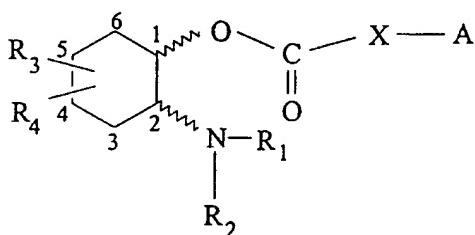
R_3 and R_4 are defined as in claim 1; and

10 A is defined as in claim 1;

with the proviso that, when X is $-(CH_2)_n-Y-$, and $n = 1$, and Y is a direct bond, and R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R_3 and R_4 are hydrogen, A may not be 4-thianaphthenyl.

- 15 3. An enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

20



(I)

30

wherein X is $-(CH_2)_n-Y-$, where $n = 1$ and Y is a direct bond or O; or $-CH(R_{12})-$, where R_{12} is alkyl of from one to six carbon atoms;

35

R_1 and R_2 are defined as in claim 1;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

40

A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from:

45

formula III of claim 1 where R_5 , R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl;

45

or formula IV of claim 1 where R_8 and R_9 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

50

or formula V of claim 1 where R_8 and R_9 are defined as above;

50

or formula VI of claim 1 where R_{10} is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH_2 , O, S, or $N-R_{11}$ where R_{11} is hydrogen or alkyl of one to six carbon atoms;

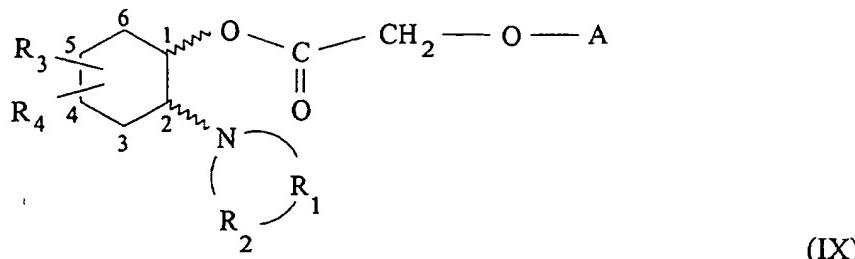
55

with the proviso that, when X is $-(CH_2)_n-Y-$, and $n = 1$, and Y is a direct bond, and R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R_3 and R_4 are hydrogen, A may not be 4-thianaphthenyl.

4. An enantiomer or geometric isomer of a compound of formula IX, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

5

10



15

wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached,

20

form a ring according to formula II of claim 1, where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

25

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring forming atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

30

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

35

R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5- positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring; and

A is a saturated carbocyclic ring of three to six carbon atoms, or is selected from:

40

formula III of claim 1 where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;

45

or formula IV of claim 1 where R₈ and R₉ are hydrogen;

or formula V of claim 1 where R₈ and R₉ are hydrogen;

or formula VI of claim 1 where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁

50

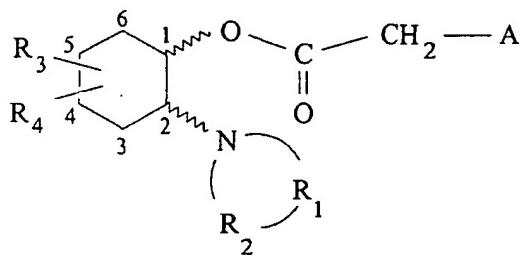
where R₁₁ is hydrogen or methyl.

5. An enantiomer or geometric isomer of a compound of formula X, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

55

55

5



10

(X)

wherein R₁ and R₂ are defined as in claim 4;

15

R₃ and R₄ are defined as in claim 4; and

A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

20

formula III of claim 1 where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;

or formula IV of claim 1 where R₈ and R₉ are hydrogen;

25

or formula V of claim 1 where R₈ and R₉ are hydrogen;

or formula VI of claim 1 where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl;

30

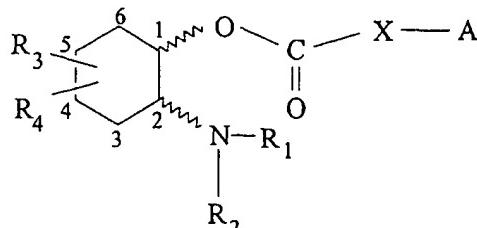
with the proviso that when R₁ and R₂, taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, and R₃ and R₄ are hydrogen, A may not be 4-thianaphthetyl.

35

6. An enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

35

40



45

(I)

wherein X is a direct bond or -CH=CH-;

50

R₁ and R₂ are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

55

or R₁ and R₂, when taken together with the nitrogen atom to which they are attached,

form a ring denoted by formula II of claim 1 where m is an integer from three to eight;

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently hydrogen, methoxy, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

5 A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

formula III of claim 1 where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, methyl or ethyl, and at least one of R_6 and R_7 is a substituent other than hydrogen;

10 or formula IV of claim 1 where R_8 and R_9 are hydrogen;

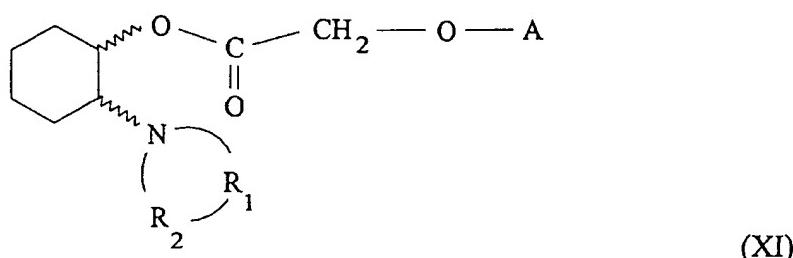
or formula V of claim 1 where R_8 and R_9 are hydrogen;

15 or formula VI of claim 1 where R_{10} is hydrogen, and Z is O, S, or N- R_{11} where R_{11} is hydrogen or methyl;

or formula VII of claim 1 when X is a direct bond;

20 or formula VIII of claim 1 when X is a direct bond.

25 7. An enantiomer or geometric isomer of a compound of formula XI, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:



35 wherein R_1 and R_2 , when taken together with the nitrogen atom to which they are attached, form a ring according to formula II of claim 1 where m is an integer from three to eight; and

A is selected from:

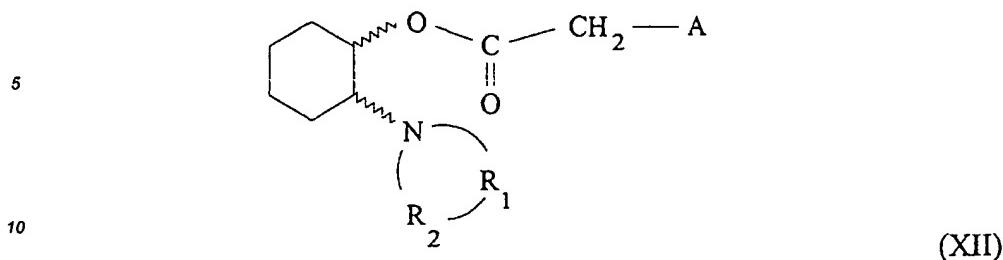
40 formula III of claim 1 where R_5 is hydrogen, and R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R_6 and R_7 is a substituent other than hydrogen;

45 or formula IV of claim 1 where R_8 and R_9 are hydrogen;

or formula V of claim 1 where R_8 and R_9 are hydrogen;

50 or formula VI of claim 1 where R_{10} is hydrogen, and Z is O or S.

55 8. An enantiomer or geometric isomer of a compound of formula XII, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:



15 wherein R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring according to formula II of claim 1 where m is an integer from three to eight; and

A is selected from:

20 formula III of claim 1 where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy, and at least one of R₆ and R₇ is a substituent other than hydrogen;

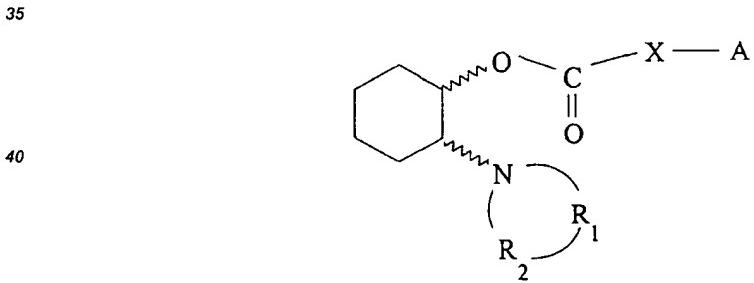
or formula IV of claim 1 where R₈ and R₉ are hydrogen;

25 or formula V of claim 1 where R₈ and R₉ are hydrogen;

or formula VI of claim 1 where R₁₀ is hydrogen, and Z is O or S;

30 with the proviso that, when R₁ and R₂ taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring, A may not be 4-thianaphthyl.

9. An enantiomer or geometric isomer of a compound of formula XIII, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:



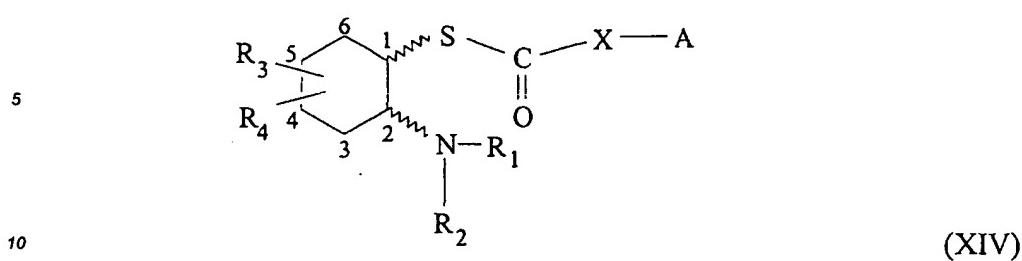
45

wherein X is a direct bond, *trans*-CH=CH-, -CH₂- or -CH₂-O-;

50 R₁ and R₂, when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, piperidinyl, hexahydroazepinyl, morpholinyl, methylpiperazinyl or 3-azabicyclo[3.2.2]nona-nyl; and

55 A is selected from cyclohexyl, 3,4-dichlorophenyl, 4-bromophenyl, 1-naphthyl, 2-naphthyl or 3-thianaphthyl.

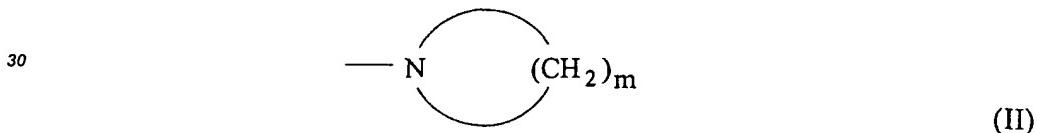
10. An enantiomer or geometric isomer of a compound of formula XIV, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:



wherein X is a direct bond;

15 or $-(CH_2)_n-Y-$, where n = 1, 2, or 3, and Y is a direct bond, O or S;
 or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S;
 or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

20 R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;
 or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached,
 25 form a ring denoted by formula II:



35 where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

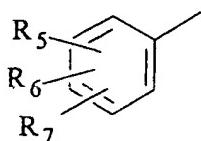
40 or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

45 or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

50 R_3 and R_4 are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII;

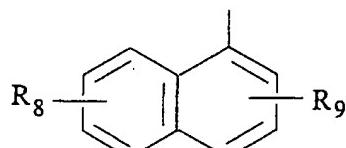
5



(III)

where R₅, R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl, and when X is a direct bond at least one of R₅, R₆ and R₇ is a substituent other than hydrogen;

15

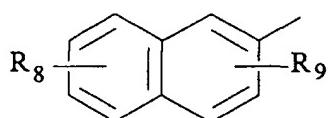


(IV)

20

where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

25

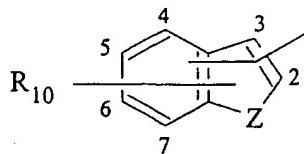


(V)

30

where R₈ and R₉ are defined as above;

35



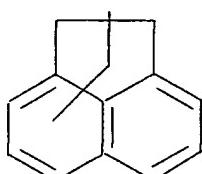
(VI)

40

where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

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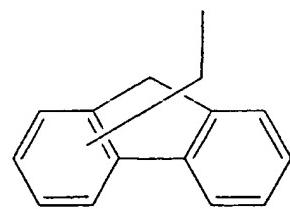


(VII)

only when X is a direct bond;

55

5



(VIII)

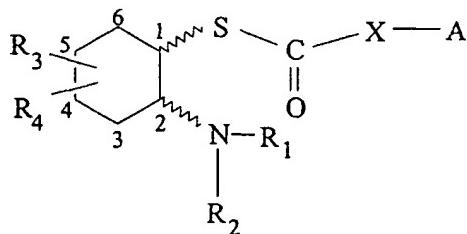
10

only when X is a direct bond.

11. An enantiomer or geometric isomer of a compound of formula XIV, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

15

20



(XIV)

25

wherein X is a direct bond;

30

- or $-(CH_2)_n-Y-$, where $n = 1$, and Y is a direct bond, O or S;
- or $-CH(R_{12})-$, where R_{12} is alkyl of from one to six carbon atoms;
- or $-C(R_{13})=CH-$, where R_{13} is hydrogen;

35

R_1 and R_2 are defined as in claim 10;

36

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5- positions, and are independently hydrogen, alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen atom; and

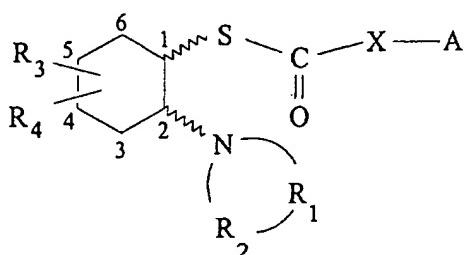
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A is defined as in claim 10.

12. An enantiomer or geometric isomer of a compound of formula XV, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

45

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(XV)

55

wherein X is $-CH_2-$ or $-CH_2-O-$;

R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring according to formula II of claim 10, where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

5

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring forming atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

10

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

15

R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5- positions, and are independently hydrogen, methoxy, or are points of attachment of a five-membered oxaspiran ring; and

A is a saturated carbocyclic ring of from three to six carbon atoms, or is selected from:

20

formula III of claim 10 where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy;

or formula IV of claim 10 where R₈ and R₉ are hydrogen;

25

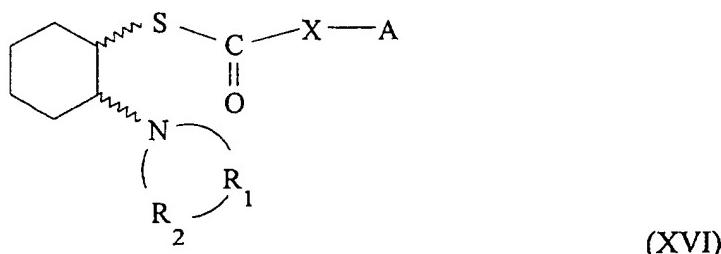
or formula V of claim 10 where R₈ and R₉ are hydrogen;

or formula VI of claim 10 where R₁₀ is hydrogen, and Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or methyl.

30

13. An enantiomer or geometric isomer of a compound of formula XVI, or a solvate or pharmaceutically acceptable salt thereof, said compound of the formula:

35



45

wherein X is a -CH₂- or -CH₂-O-;

R₁ and R₂, when taken together with the nitrogen atom to which they are attached, form a ring according to formula II of claim 10 where m is an integer from three to eight; and

50

A is selected from:

formula III of claim 10 where R₅ is hydrogen, and R₆ and R₇ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, methyl, ethyl, methoxy, or ethoxy;

55

or formula IV of claim 10 where R₈ and R₉ are hydrogen;

or formula V of claim 10 where R₈ and R₉ are hydrogen;

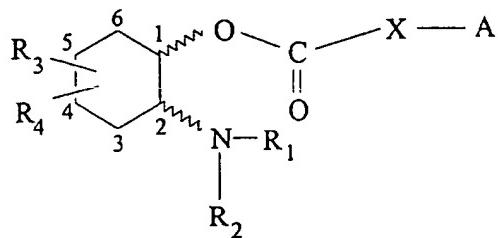
or formula VI of claim 10 where R₁₀ is hydrogen, and Z is O or S.

14. A compound selected from the group consisting of:

- 5 (±)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](3,4-dichlorophenoxy)acetate;
- (±)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](1-naphthoxy)acetate;
- (±)-*trans*-{2-[N-(3-azabicyclo[3.2.2]nonyl)]cyclohexyl}(3,4-dichlorophenoxy)acetate; (±)-*trans*-{2-(4-morpholiny)cyclohexyl}(3,4-dichlorophenoxy)acetate;
- 10 (±)-*trans*-[2-(1-hexahydroazepinyl)cyclohexyl](3,4-dichlorophenoxy)acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]benzo[b]thiophene-3-acetate;
- (±)-*trans*-[2-(1-pyrrolidinyl)cyclohexyl](cyclohexyl)acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]naphthyl-1-acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]naphthyl-2-acetate;
- 15 (±)-*trans*-[2-(4-morpholiny)cyclohexyl]phenylacetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl](3,4-dichlorophenyl)acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl](4-nitrophenyl)acetate;
- (±)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexyl]naphthyl-2-acetate;
- (±)-*trans*-[2-(4-methyl-1-piperazinyl)cyclohexyl]naphthyl-1-acetate;
- 20 (±)-*trans*-[2-(4-morpholiny)cyclohexyl]-1-naphthoate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]benzo[b]thiophene-4-acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl](4-bromophenyl)acetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]-3,4-dichlorocinnamate;
- (±)-*trans*-[2-(1-piperidinyl)cyclohexyl]thiophenoxyacetate;
- 25 (±)-*trans*-[2-(4-morpholiny)cyclohexyl]-2-(1-naphthyl)propionate;
- (±)-(1 α ,2 β ,4 β ,5 β)-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzofuran-2-acetate;
- (±)-*trans*-{2-[bis(2-methoxyethyl)amino]cyclohexyl}fluorene-9-carboxylate;
- S- {(±)-*trans*-[2-(4-morpholiny)cyclohexyl]} naphthyl-1-thioacetate;
- S-{(±)-*trans*-{2-[bis(2-methoxyethyl)amino]cyclohexyl}}-4-bromothiobenzoate;
- 30 (±)-*trans*-[2-(diisopropylamino)cyclohexyl]acenaphthene-1-carboxylate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]diphenylacetate;
- (±)-*trans*-[2-(4-morpholiny)cyclohexyl]-3-trifluoromethylbenzoate;
- [7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]naphthyl-1-acetate;
- S- {(±)-*trans*-[2-(4-morpholiny)cyclohexyl]}(3,4-dimethoxyphenyl)thioacetate; and pharmaceutically acceptable salts thereof.

- 35 **15. A composition comprising a compound according to any one of claims 1-14 in combination with a pharmaceutically acceptable carrier or diluent.**
- 40 **16. A compound according to any one of claims 1-9 and 14 for use in a method for treating arrhythmia in a warm-blooded animal.**
- 45 **17. A compound according to any one of claims 1-9 and 14 for use in a method for blocking ion channels in a warm-blooded animal.**
- 50 **18. A compound according to any one of claims 10-13 for use in a method for treating arrhythmia in a warm-blooded animal.**
- 19. A compound according to any one of claims 10-13 for use in a method for blocking ion channels in a warm-blooded animal.**
- 20. A compound according to any one of claims 1-14 for use in a method for blocking ion channels *in vitro*.**
- 55 **21. Use of an enantiomer or geometric isomer of a compound of formula I, or a solvate or pharmaceutically acceptable salt thereof, in the manufacture of a medicament to treat arrhythmia, said compound of the formula:**

5



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(I)

wherein X is a direct bond;

15

or $-(CH_2)_n-Y-$, where $n = 1, 2$, or 3 , and Y is a direct bond, O or S;
 or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S;
 or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

20

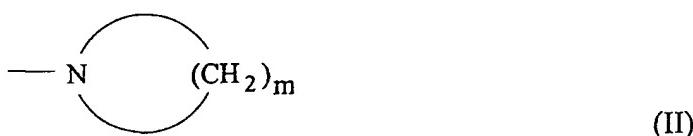
R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

25

or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached,

form a ring denoted by formula II:

30



(II)

35

where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

40

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

45

or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

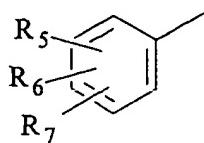
50

R_3 and R_4 are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII;

55

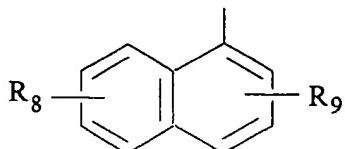
5



(III)

where R_5 , R_6 and R_7 are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl;

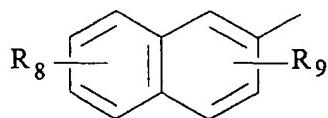
15



(IV)

where R_8 and R_9 are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

25

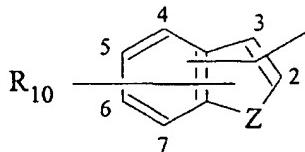


(V)

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where R_8 and R_9 are defined as above;

35



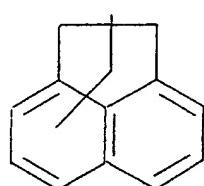
(VI)

40

where R_{10} is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH_2 , O, S, or N- R_{11} where R_{11} is hydrogen or alkyl of one to six carbon atoms;

45

50

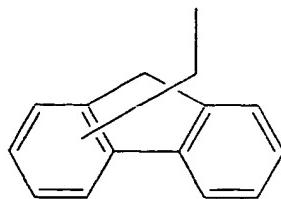


(VII)

55

only when X is a direct bond;

5



(VIII)

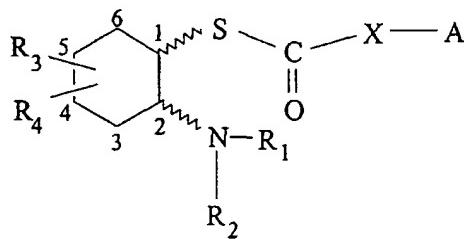
10

only when X is a direct bond.

22. Use of an enantiomer or geometric isomer of a compound of formula XIV, or a solvate or pharmaceutically acceptable salt thereof, in the manufacture of a medicament to treat arrhythmia, said compound of the formula:

15

20



(XIV)

25

wherein X is a direct bond;

30

or $-(CH_2)_n-Y-$, where $n = 1, 2$, or 3 , and Y is a direct bond, O or S;
or $-CH(R_{12})-Y-$, where R_{12} is alkyl of from one to six carbon atoms, a saturated carbocyclic ring of from three to six carbon atoms, phenyl or benzyl, and Y is a direct bond, O or S;
or $-C(R_{13})=CH-$, where R_{13} is hydrogen, alkyl of from one to six carbon atoms, or phenyl;

35

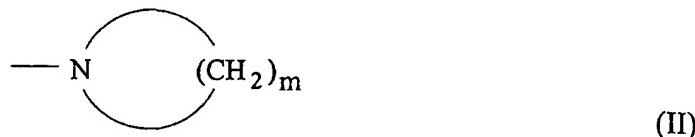
R_1 and R_2 are independently hydrogen, alkyl of three to eight carbon atoms, alkoxyalkyl of three to eight carbon atoms, or aralkyl of seven to twelve carbon atoms;

or R_1 and R_2 , when taken together with the nitrogen atom to which they are attached,

40

form a ring denoted by formula II:

45



50

where m is an integer from three to eight, and said ring may be substituted at any one carbon atom by hydroxy, oxo, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms, or may be fused at two adjacent carbon atoms with an aromatic or aliphatic carbocyclic ring of six carbon atoms;

55

or complete a saturated monocyclic nitrogen heterocyclic ring of five to eight ring atoms, containing only carbon, nitrogen and optionally oxygen ring atoms, and said heterocyclic ring containing not more than two nitrogen ring atoms, the second nitrogen being optionally substituted with an alkyl group of one to six carbon atoms or a phenyl ring;

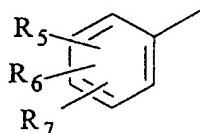
or complete a ring selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, or 3-azabicyclo[3.2.0]heptan-3-yl;

5 R₃ and R₄ are independently attached to the cyclohexane ring at the 3-, 4-, 5-, or 6-positions, and are independently hydrogen, hydroxy, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, or are points of attachment of a spiro five- or six-membered heterocyclic ring containing one oxygen or sulfur atom; and

A is an alkyl group of five to twelve carbon atoms, or is a saturated carbocyclic ring of three to six carbon atoms, or is selected from formulae III, IV, V, VI, VII or VIII:

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15

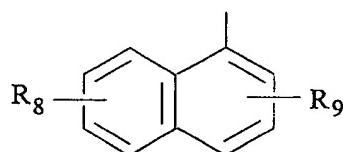


(III)

20

where R₅, R₆ and R₇ are independently hydrogen, hydroxy, amino, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, or aryl;

25

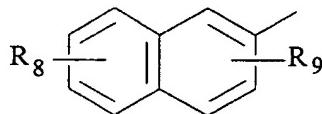


(IV)

30

where R₈ and R₉ are independently hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms or aryl;

35

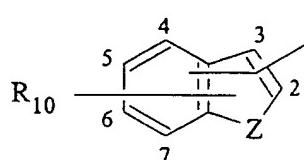


(V)

40

where R₈ and R₉ are defined as above;

45



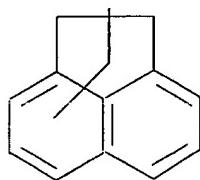
(VI)

50

where R₁₀ is hydrogen, hydroxy, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl; Z is CH₂, O, S, or N-R₁₁ where R₁₁ is hydrogen or alkyl of one to six carbon atoms;

55

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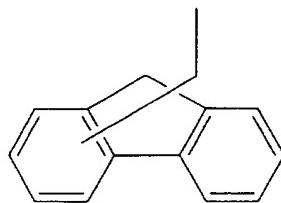


(VII)

10

only when X is a direct bond;

15



(VIII)

20

only when X is a direct bond.

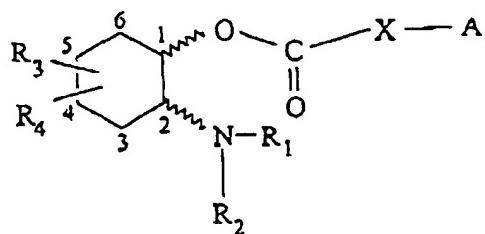
25

Patentansprüche

- Enantiomer oder geometrisches Isomer einer Verbindung der Formel I oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung folgende Formel aufweist:

30

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(I)

40

worin X eine direkte Bindung ist;

45

- oder $-(\text{CH}_2)_n-\text{Y}$ - ist, wobei $n = 1, 2$ oder 3 ist und Y eine direkte Bindung, O oder S ist;
 oder $-\text{CH}(\text{R}_{12})-\text{Y}$ -, wobei R_{12} ein Alkyl von einem bis sechs Kohlenstoffatomen, ein gesättigter Carboxytring aus von drei bis sechs Kohlenstoffatomen, Phenyl oder Benzyl ist und Y eine direkte Bindung, O oder S ist;
 oder $-\text{C}(\text{R}_{13})=\text{CH}-$, wobei R_{13} Wasserstoff, Alkyl aus von einem bis sechs Kohlenstoffatomen oder Phenyl ist;

50

R_1 und R_2 unabhängig voneinander Wasserstoff, Alkyl von drei bis acht Kohlenstoffatomen, Alkoxyalkyl von drei bis acht Kohlenstoffatomen oder Aralkyl von sieben bis zwölf Kohlenstoffatomen sind;

oder R_1 und R_2 , wenn mit dem Stickstoffatom zusammengenommen, an das sie angebunden sind, einen Ring bilden, der durch die Formel II angegeben ist:

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5



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wobei m eine ganze Zahl von drei bis acht ist und der Ring an jedem Kohlenstoffatom durch Hydroxy, Oxo, Alkyl von einem bis drei Kohlenstoffatomen oder Alkoxy von einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzende Kohlenstoffatome mit einem aromatischen oder aliphatischen Carboxylring von sechs Kohlenstoffatomen fusioniert sein kann;

15

oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring von fünf bis acht Ringatomen vervollständigen, der nur Kohlenstoff, Stickstoff und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-Ringatome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe von einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist,

20

oder einen Ring, ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2.]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

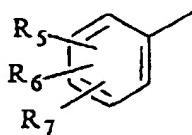
25

R₃ und R₄ unabhängig voneinander an den Cyclohexanring an den 3-, 4-, 5- oder 6-Positionen angebracht sind und unabhängig voneinander Wasserstoff, Hydroxy, Alkyl von einem bis sechs Kohlenstoffatomen oder Alkoxy von einem bis sechs Kohlenstoffatomen sind oder Anbindungspunkte eines Spiro-fünf- oder sechsgliedrigen heterozyklischen Ringes sind, der ein Sauerstoff- oder Schwefelatom enthält; und

30

A eine Alkylgruppe von fünf bis zwölf Kohlenstoffatomen ist oder ein gesättigter Carboxytring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt aus Formeln III, IV, V, VI, VII oder VIII ist:

35



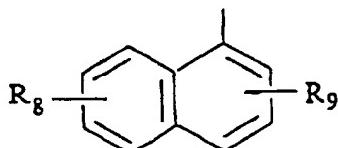
(III)

40

wobei R₅, R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind und wenn X eine direkte Bindung ist, ist mindestens einer von R₅, R₆ und R₇ Hydroxy, Fluor, Chlor, Brom, Trifluormethyl, Alkyl aus von einem bis sechs Kohlenstoffatomen oder Aryl-substituent und wenn X -CH=CH- ist, und R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie angebunden sind, einen N-Phenylpiperazinring bilden und R₃ und R₄ Wasserstoff sind, ist eines von R₅, R₆ und R₇ ein anderer Substituent als Wasserstoff;

45

50

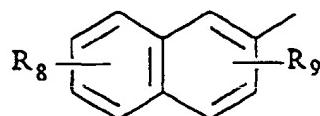


(IV)

55

wobei R₈ und R₉ unabhängig voneinander Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

5

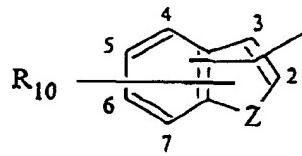


(V)

10

wobei R₈ und R₉ wie oben definiert sind;

15



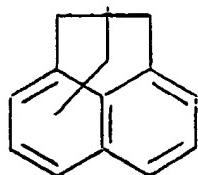
(VI)

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wobei R₁₀ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl ist; Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Alkyl von einem bis sechs Kohlenstoffatomen ist;

25

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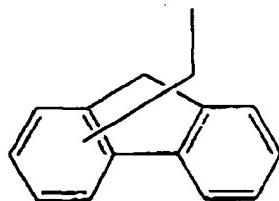


(VII)

35

nur wenn X eine direkte Bindung ist;

40



(VIII)

45

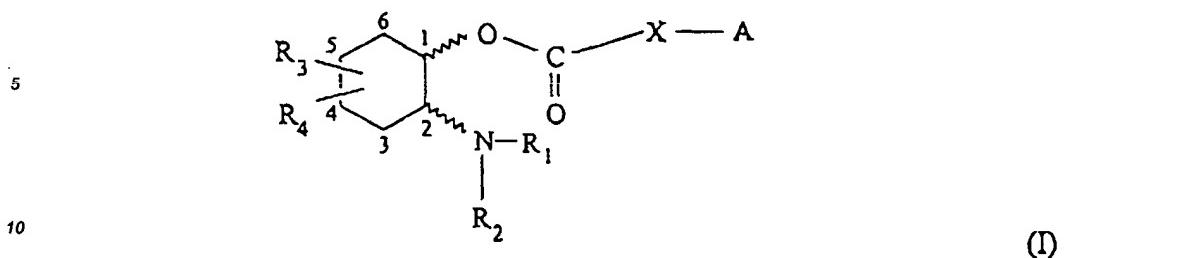
nur wenn X eine direkte Bindung ist;

50

unter der Voraussetzung, daß wenn X -(CH₂)_n-Y- ist und n = 1 ist und Y eine direkte Bindung ist und R₁ und R₂, wenn zusammen mit dem Stickstoffatom genommen an das sie angebunden sind einen Pyrrolidinylring bilden und R₃ und R₄ Wasserstoff sind, A nicht 4-Thianaphthetyl sein kann.

2. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel I, oder ein Solvat oder ein pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

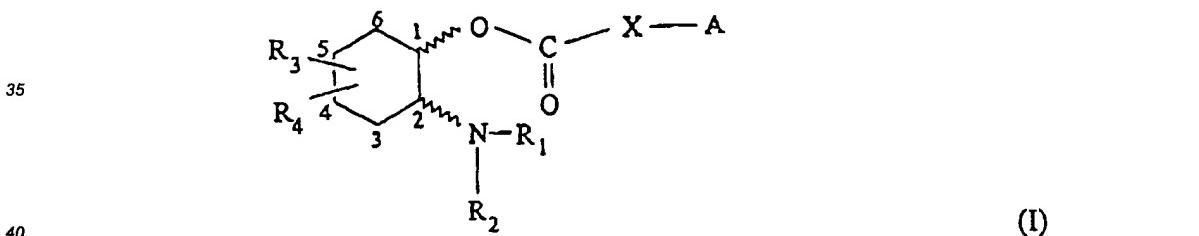
55



worin X eine direkte Bindung ist;

- 15 oder $-(CH_2)_n-Y-$, wobei $n = 1$ und Y eine direkte Bindung, O oder S ist;
oder $-CH(R_{12})-$, wobei R_{12} Alkyl von einem bis sechs Kohlenstoffatomen ist;
oder $-C(R_{13})=CH-$, wobei R_{13} Wasserstoff ist;
- 20 R_1 und R_2 wie in Anspruch 1 definiert sind;
- 25 R_3 und R_4 wie in Anspruch 1 definiert sind; und
 A wie in Anspruch 1 definiert ist;
- 30 unter der Voraussetzung, daß wenn $X-(CH_2)_n-Y-$ ist und $n = 1$ ist und Y eine direkte Bindung ist und R_1 und R_2 , wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidinylingen und R_3 und R_4 Wasserstoff sind, A nicht 4-Thianaphthetyl sein kann.

3. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel I oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung folgende Formel aufweist:



worin $X-(CH_2)_n-Y-$ ist, wobei $n = 1$ und Y eine direkte Bindung oder O ist;
oder $-CH(R_{12})-$, wobei R_{12} Alkyl aus von einem bis sechs Kohlenstoffatomen ist;
 R_1 und R_2 wie in Anspruch 1 definiert sind;

- 45 R_3 und R_4 unabhängig voneinander angebunden an den Cyclohexanring an den 4- oder 5-Positionen sind und unabhängig voneinander Wasserstoff, Alkoxy aus einem bis sechs Kohlenstoffatomen sind oder Ansatzpunkte eines Spiro-fünf- oder sechs-gliedrigen heterozyklischen Rings sind, der ein Sauerstoffatom enthält; und
- 50 A eine Alkoxygruppe von fünf bis zwölf Kohlenstoffatomen ist oder ein gesättigter heterozyklischer Ring aus drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus:

- 55 Formel III nach Anspruch I, wobei R_5 , R_6 und R_7 unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

oder Formel IV nach Anspruch 1, wobei R_8 und R_9 unabhängig voneinander Wasserstoff, Hydroxy, Fluor,

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Chlor, Brom, Alkyl aus einem von einem bis sechs Kohlenstoffatomen, Alkoxy aus einem bis sechs Kohlenstoffatomen oder Aryl sind;

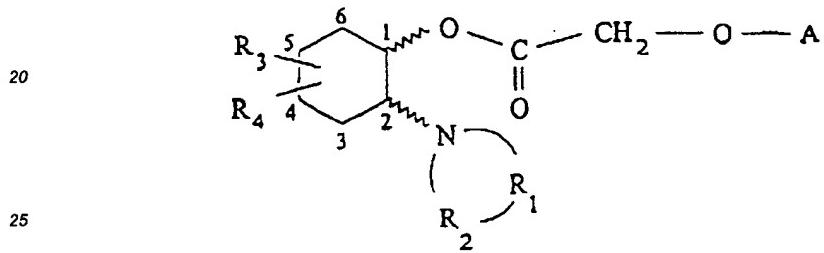
oder Formel V nach Anspruch 1, wobei R₈ und R₉ wie oben definiert sind;

5

oder Formel VI nach Anspruch 1, wobei R₁₀ Wasserstoff, Hydroxy, Chlor, Fluor, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy aus von einem bis sechs Kohlenstoffatomen oder Aryl ist; Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Alkyl aus einem bis sechs Kohlenstoffatomen ist;

10 unter der Voraussetzung, daß, wenn X -(CH₂)_n-Y- und n = 1 ist und Y eine direkte Bindung ist und R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidinyrling bilden und R₃ und R₄ Wasserstoff sind, A nicht 4-Thianaphthetyl sein kann.

15 4. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel IX oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:



worin R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind,

30

einen Ring nach Formel II nach Anspruch 1 bilden, wobei m eine ganze Zahl von drei bis acht ist und der Ring an irgendeinem Kunststoffatom durch Hydroxy, Oxo, Alkyl aus einem bis drei Kohlenstoffatomen oder Alkoxy aus einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzenden Kohlenstoffatomen mit einem aromatischen oder aliphatischen Carboxyrling von sechs Kohlenstoffatomen fusioniert sein kann.

35

oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring aus fünf bis acht Ringatomen vervollständigen, der nur Kohlenstoff, Stickstoffe und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-ringbildende Atome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe aus einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist;

40

oder einen Ring ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

45

R₃ und R₄ unabhängig voneinander an den 4- oder 5-Positionen an den Cyclohexanring angebunden sind und unabhängig voneinander Wasserstoff, Methoxy sind oder Anbindungspunkte eines 5-gliedrigen Oxaspiranringes sind; und

50

A ein gesättigter Carboxyrling von drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus:

55

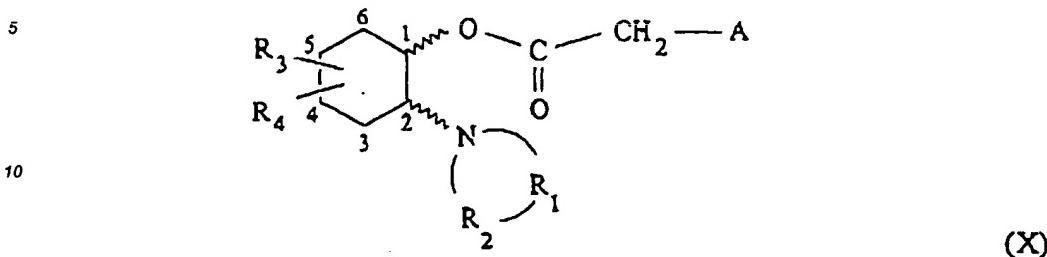
Formel III nach Anspruch 1, wobei R₅ Wasserstoff ist und R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind und mindestens einer von R₆ und R₇ ein Substituent anders als Wasserstoff ist;

55

oder Formel IV nach Anspruch 1, wobei R₈ und R₉ Wasserstoff sind;

oder Formel V nach Anspruch 1, wobei R₈ und R₉ Wasserstoff sind und Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Methyl ist

5. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel X oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:



15 worin R₁ und R₂ wie in Anspruch 4 definiert sind;

R₃ und R₄ wie in Anspruch 4 definiert sind; und

A ein gesättigter Carboxyring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus:

20 Formel III nach Anspruch 1, wobei R₅ Wasserstoff ist und R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind und mindestens einer von R₆ und R₇ ein Substituent anders als Wasserstoff ist;

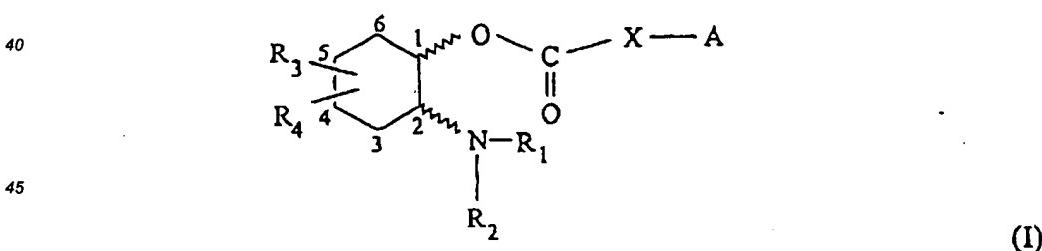
25 oder Formel IV nach Anspruch 1, wobei R₈ und R₉ Wasserstoff sind;

oder Formel V nach Anspruch 1, wobei R₈ und R₉ Wasserstoff sind;

30 oder Formel VI nach Anspruch 1, wobei R₁₀ Wasserstoff ist und Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Methyl ist;

unter der Voraussetzung, daß, wenn R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidinylingen bilden und R₃ und R₄ Wasserstoff sind, A nicht 4-Thianaphthenyl sein kann.

- 35 6. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel I oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:



worin X eine direkte Bindung ist;

50 R₁ und R₂ unabhängig von einander Wasserstoff, Alkyl von drei bis acht Kohlenstoffatomen, Alkoxyalkyl von drei bis acht Kohlenstoffatomen oder Aralkyl von sieben bis zwölf Kohlenstoffatomen sind;

55 oder R₁ und R₂, wenn mit dem Stickstoffatom zusammengenommen, an das sie angebunden sind, einen Ring bilden, der durch die Formel II nach Anspruch 1 angegeben ist:

oder einen Ring ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

R_3 und R_4 unabhängig voneinander an den 4- oder 5-Positionen an den Cyclohexanring angebracht sind und unabhängig voneinander Wasserstoff, Methoxy sind oder Ansatzpunkte eines Spiro 5- oder 6-gliedrigen heterocyclischen Rings sind, der ein Sauerstoffatom enthält; und

5 A ein gesättigter Carboxyring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus:

Formel III nach Anspruch 1, wobei R_5 Wasserstoff ist und R_6 und R_7 unabhängig von einander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind und mindestens einer von R_6 und R_7 ein Substituent anders als Wasserstoff ist;

10 oder Formel IV nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

oder Formel V nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

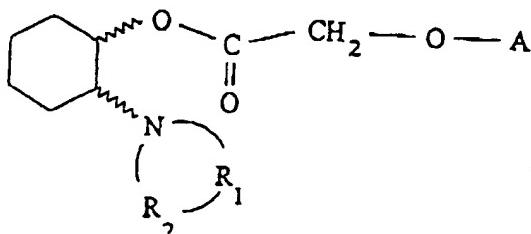
15 oder Formel VI nach Anspruch 1, wobei R_{10} Wasserstoff ist und Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Methyl ist;

oder Formel VII nach Anspruch 1, wenn X eine direkte Bindung ist;

20 oder Formel VIII nach Anspruch 1, wenn X eine direkte Bindung ist.

7. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel XI oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

25



(XI)

30

worin R₁ und R₂ wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, ein Ring nach Formel II nach Anspruch 1 bilden, wobei m eine ganze Zahl von drei bis acht ist; und

40 A ausgewählt ist aus:

Formel III nach Anspruch 1, wobei R_5 Wasserstoff ist und R_6 und R_7 unabhängig von einander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind und mindestens einer von R_6 und R_7 ein Substituent anders als Wasserstoff ist;

45 oder Formel IV nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

oder Formel V nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

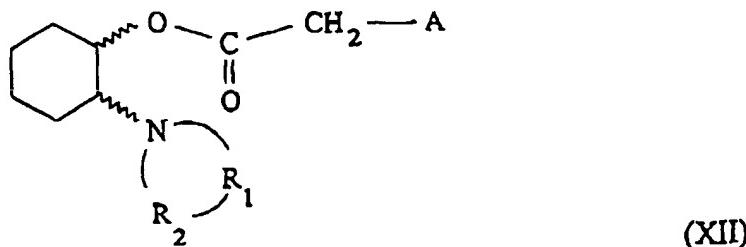
50 oder Formel VI nach Anspruch 1, wobei R_{10} Wasserstoff ist und Z O oder S ist.

8. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel XII oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

55

5

10



worin R_1 und R_2 , wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, ein Ring nach Formel II nach Anspruch 1 bilden, wobei m eine ganze Zahl von drei bis acht ist; und

15

A ausgewählt ist aus:

20

Formel III nach Anspruch 1, wobei R_5 Wasserstoff ist und R_6 und R_7 unabhängig von einander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind und mindestens einer von R_6 und R_7 ein Substituent anders als Wasserstoff ist;

oder Formel IV nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

25

oder Formel V nach Anspruch 1, wobei R_8 und R_9 Wasserstoff sind;

oder Formel VI nach Anspruch 1, wobei R_{10} Wasserstoff ist und Z O oder S ist,

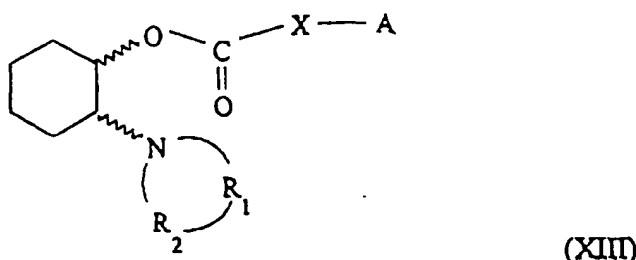
unter der Voraussetzung, daß, wenn R_1 und R_2 , wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidinyrring bilden, A nicht 4-Thianaphthenyl sein kann.

30

9. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel XII oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

35

40



45

worin X eine direkte Bindung, trans-CH=CH-, -CH₂- oder -CH₂-O- ist;

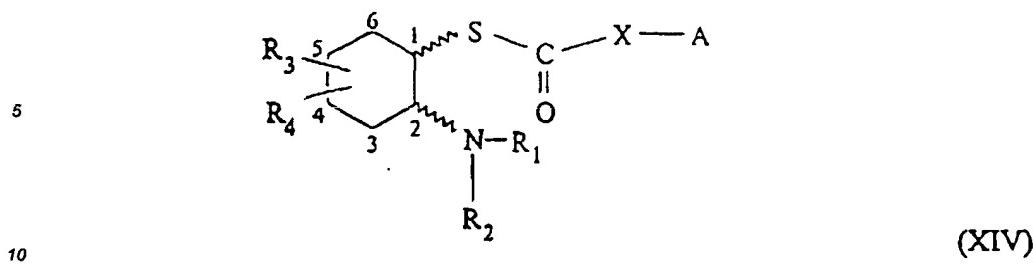
50

R_1 und R_2 , wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, einen Ring ausgewählt aus Pyrrolidinyl, Hexahydroazepinyl, Morpholinyl, Methylpiperazinyl oder 3-Azabicyclo[3.2.2]nonanyl vervollständigen; und

A ausgewählt ist aus Cyclohexyl, 3,4-Dichlorphenyl, 4-Bromphenyl, 1-Naphthyl oder 3-Thianaphthenyl.

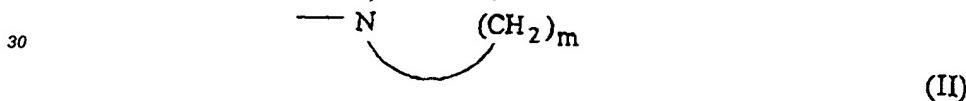
55

10. Enantiomer oder geometrisches Isomer einer Verbindung der Formel I oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung folgende Formel aufweist;



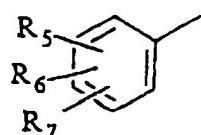
worin X eine direkte Bindung ist;

- 15 oder $-(CH_2)_n-Y-$ ist, wobei $n = 1, 2$ oder 3 ist und Y eine direkte Bindung, O oder S ist;
 oder $-CH(R_{12})-Y-$, wobei R_{12} ein Alkyl von einem bis sechs Kohlenstoffatomen, ein gesättigter Carboxytring aus von drei bis sechs Kohlenstoffatomen, Phenyl oder Benzyl ist und Y eine direkte Bindung, O oder S ist;
 oder $-C(R_{13})=CH-$, wobei R_{13} Wasserstoff, Alkyl aus von einem bis sechs Kohlenstoffatomen oder Phenyl ist;
- 20 R_1 und R_2 unabhängig voneinander Wasserstoff, Alkyl von drei bis acht Kohlenstoffatomen, Alkoxyalkyl von drei bis acht Kohlenstoffatomen oder Aralkyl von sieben bis zwölf Kohlenstoffatomen sind;
 oder R_1 und R_2 , wenn mit dem Stickstoffatom zusammengenommen, an das sie angebunden sind,
- 25 einen Ring bilden der durch die Formel II angegeben ist:



- 35 wobei m eine ganze Zahl von drei bis acht ist und der Ring an jedem Kohlenstoffatom durch Hydroxy, Oxo, Alkyl von einem bis drei Kohlenstoffatomen oder Alkoxy von einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzenden Kohlenstoffatomen mit einem aromatischen oder aliphatischen Carboxyl von sechs Kohlenstoffatomen fusioniert sein kann;
- 40 oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring von fünf bis acht Ringatomen vervollständigt, der nur Kohlenstoff, Stickstoff und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-Ringatome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe von einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist;
- 45 oder einem Ring ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2.]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigt;
- 50 R_3 und R_4 unabhängig voneinander an den Cyclohexanring an den 3-, 4-, 5- oder 6-Positionen angebracht sind und unabhängig voneinander Wasserstoff, Hydroxy, Alkyl von einem bis sechs Kohlenstoffatomen oder Alkoxy aus von einem bis sechs Kohlenstoffatomen sind oder Anbindungspunkte eines Spiro-fünf- oder sechsgliedrigen heterozyklischen Rings sind, der ein Sauerstoff oder Schwefelatom enthält; und
- A eine Alkylgruppe von fünf bis zwölf Kohlenstoffatomen ist oder ein gesättigter Carboxytring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus Formeln III, IV, V, VI, VII oder VIII:
- 55

5



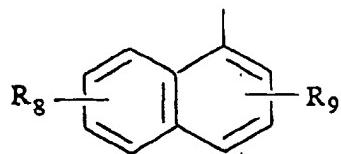
(III)

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wobei R₅, R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy aus einem bis sechs Kohlenstoffatomen oder Aryl sind, und, wenn X eine direkte Bindung ist, ist mindestens eines von R₅, R₆ und R₇ ein anderer Substituent als Wasserstoff;

15

20

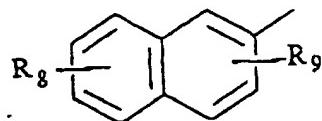


(IV)

25

wobei R₈ und R₉ unabhängig von einander Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

30

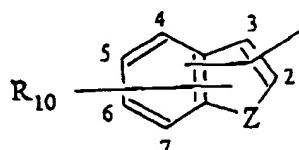


(V)

35

wobei R₈ und R₉ wie oben definiert sind;

40



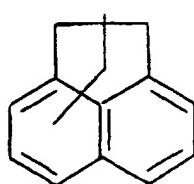
(VI)

45

wobei R₁₀ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl ist; Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Alkyl von einem bis sechs Kohlenstoffatomen ist;

50

55

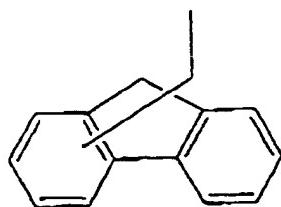


(VII)

nur wenn X eine direkte Bindung ist;

5

10



(VIII)

15

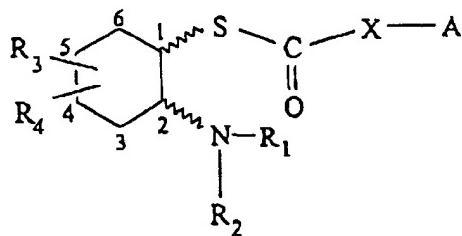
nur wenn X eine direkte Bindung ist.

15

11. Enantiomer oder geometrisches Isomer einer Verbindung der Formel XIV oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung folgende Formel aufweist:

20

25



(XIV)

30

worin X eine direkte Bindung ist;

35

oder $-(CH_2)_n-Y$ ist, wobei $n = 1$ ist und Y eine direkte Bindung, O oder S ist;
oder $-CH(R_{12})-Y$, wobei R_{12} ein Alkyl von einem bis sechs Kohlenstoffatomen ist;
oder $-C(R_{13})=CH-$, wobei R_{13} Wasserstoff ist;

R_1 und R_2 wie in Anspruch 10 definiert sind;

40

R_3 und R_4 unabhängig voneinander an den Cyclohexanring an den 4- oder 5- Positionen angebracht sind und unabhängig voneinander Wasserstoff, Hydroxy, Alkyl von einem bis sechs Kohlenstoffatomen oder Alkoxy von einem bis sechs Kohlenstoffatomen sind oder Anbindungspunkte eines Spiro fünf- oder sechs-gliedrigen heterozyklischen Rings sind, der ein Sauerstoffatom enthält; und

45

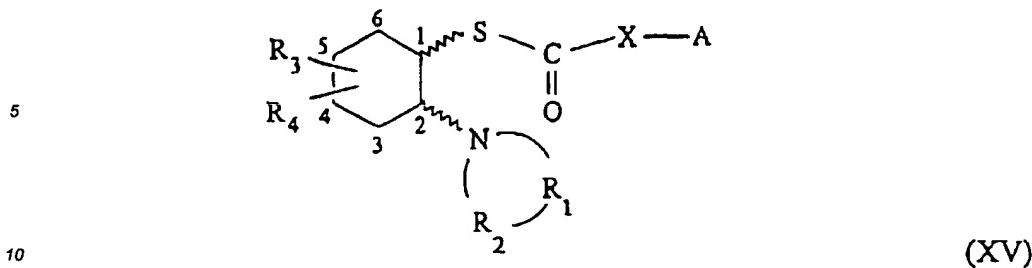
A wie in Anspruch 10 definiert ist.

45

12. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel XV oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

50

55



worin X -CH₂- oder -CH₂O- ist;

15 R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, ein Ring nach Formel II nach Anspruch 10 bilden, wobei m eine ganze Zahl von drei bis acht ist und der Ring an irgendeinem Kunststoffatombereich durch Hydroxy, Oxo, Alkyl aus einem bis drei Kohlenstoffatomen oder Alkoxy aus einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzenden Kohlenstoffatomen mit einem aromatischen oder aliphatischen Carboxytring von sechs Kohlenstoffatomen fusioniert sein kann;

20 oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring aus fünf bis acht Ringatomen vervollständigen, der nur Kohlenstoff, Stickstoff und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-ringbildende Atome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe aus einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist;

25 oder einen Ring, ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2]octan-2-yl, 3-Azabicyclo [3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

30 R₃ und R₄ unabhängig von einander an den 4- oder 5-Positionen an den Cyclohexanring angebracht sind und unabhängig voneinander Wasserstoff, Methoxy sind oder Anbindungspunkte eines 5-gliedrigen Oxaspiranrings sind; und

35 A ein gesättigter Carboxyring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt ist aus :

Formel III nach Anspruch 10, wobei R₅ Wasserstoff ist und R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind;

40 oder Formel IV nach Anspruch 10, wobei R₈ und R₉ Wasserstoff sind;

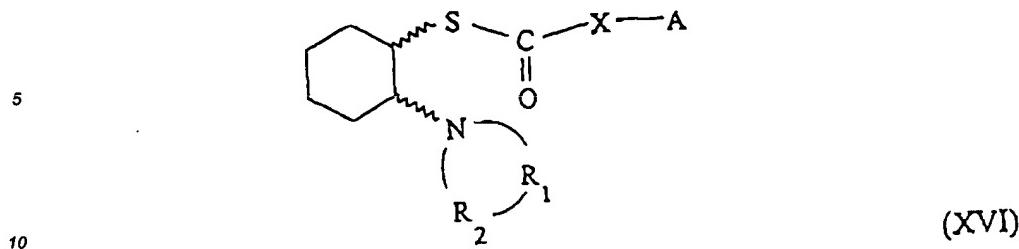
oder Formel V nach Anspruch 10, wobei R₈ und R₉ Wasserstoff sind;

oder Formel VI nach Anspruch 10, wobei R₁₀ Wasserstoff ist und Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Methyl ist.

45 13. Enantiomer oder geometrisches Isomer einer Verbindung nach Formel XVI oder ein Solvat oder pharmazeutisch akzeptables Salz davon, wobei die Verbindung die folgende Formel aufweist:

50

55



worin X -CH₂- oder -CH₂-O- ist;

- 15 R₁ und R₂, wenn zusammengenommen mit dem Stickstoffatom, an das sie gebunden sind, ein Ring nach Formel II nach Anspruch 10 bilden, wobei m eine ganze Zahl von drei bis acht ist; und
- A ausgewählt ist aus:
- 20 Formel III nach Anspruch 10, wobei R₅ Wasserstoff ist und R₆ und R₇ unabhängig von einander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Methyl, Ethyl, Methoxy oder Ethoxy sind;
- oder Formel IV nach Anspruch 10, wobei R₈ und R₉ Wasserstoff sind;
- 25 oder Formel V nach Anspruch 10, wobei R₈ und R₉ Wasserstoff sind;
- oder Formel VI nach Anspruch 10, wobei R₁₀ Wasserstoff ist und Z O oder S ist

14. Verbindung, ausgewählt aus der Gruppe bestehend aus:

- 30 (±)-trans-[2-(1-Pyrrolidinyl)cyclohexyl](3,4-dichlorphenoxy)acetat;
 (±)-trans-[2-(1-Pyrrolidinyl)cyclohexyl](1-naphthoxy)acetat;
 (±)-trans-[2-[N-(3-Azabicyclo[3.2.2]nonyl)]cyclohexyl](3,4-dichlorphenoxy)acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl](3,4-dichlorphenoxy)acetat;

35 (±)-trans-[2-(1-Hexahydroazepinyl)cyclohexyl](3,4-dichlorphenoxy)acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]benzo[b]thiophen-3-acetat;
 (±)-trans-[2-(1-Pyrrolidinyl)cyclohexyl](cyclohexyl)acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]naphthyl-1-acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]naphthyl-2-acetat;

40 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]phenylacetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl](3,4-dichlorphenyl)acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl](4-nitrophenyl)acetat;
 (±)-trans-[2-(4-Methyl-1-piperazinyl)cyclohexyl]naphthyl-2-acetat;
 (±)-trans-[2-(4-Methyl-1-piperazinyl)cyclohexyl]naphthyl-1-acetat;

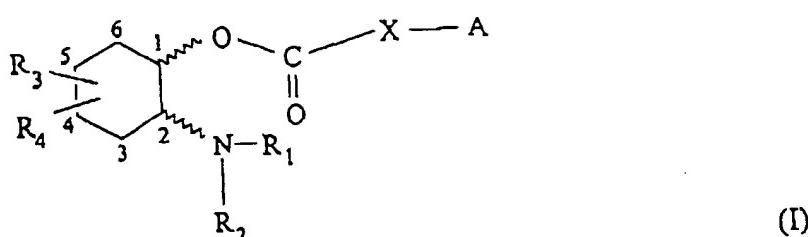
45 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]-1-aphthoat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]benzo[b]thiophen-4-acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl](4-bromphenyl)acetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]-3,4-dichlorzimtsäureester;
 (±)-trans-[2-(1-Piperidinyl)cyclohexyl]thiophenoxyacetat;

50 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]-2-(1-naphthyl)propionat;
 (±)-(1 α ,2 β ,4 β ,5 β)-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]benzofuran-2-acetat;
 (±)-trans-[2-[bis-(2-Methoxyethyl)amino]cyclohexyl]fluoren-9-carboxylat;
 S-(±)-trans-[2-(4-Morpholinyl)cyclohexyl]naphthyl-1-thioacetat;
 S-((±)-trans-[2-[bis(2-Methoxyethyl)amino]cyclohexyl]-4-bromthiobenzoat;

55 (±)-trans-[2-Diisopropylamino)cyclohexyl]acenaphthen-1-carboxylat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]diphenylacetat;
 (±)-trans-[2-(4-Morpholinyl)cyclohexyl]-3-trifluormethylbenzoat;
 [7-(Pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]naphthyl-1-acetat;

S- $\{(\pm)\text{-trans-[2-(4-Morpholinyl)cyclohexyl]}\}(3,4\text{dimethoxyphenyl})\text{thioacetat}$; und pharmazeutisch akzeptable Salze davon.

- 5 15. Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1-14 in Kombination mit einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel.
- 10 16. Zusammensetzung nach einem der Ansprüche 1-9 und 14 zur Verwendung in einem Verfahren zur Behandlung von Arrhythmia in einem warmblütigen Tier.
- 15 17. Zusammensetzung nach einem der Ansprüche 1-9 und 14 zur Verwendung in einem Verfahren zur Blockierung von Ionenkanälen in einem warmblütigen Tier.
- 20 18. Zusammensetzung nach einem der Ansprüche 10-13 zur Verwendung in einem Verfahren zur Behandlung von Arrhythmia in einem warmblütigen Tier.
- 25 19. Zusammensetzung nach einem der Ansprüche 10-13 zur Verwendung in einem Verfahren zur Blockierung von Ionenkanälen in einem warmblütigen Tier.
- 30 20. Zusammensetzung nach einem der Ansprüche 1-14 zur Verwendung in einem Verfahren zur Blockierung von Ionenkanälen *in vitro*.
- 35 21. Verwendung eines Enantiomers oder geometrischen Isomers einer Verbindung der Formel I oder eines Solvat oder pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikaments zur Behandlung von Arrhythmia, wobei die Verbindung folgende Formel aufweist:

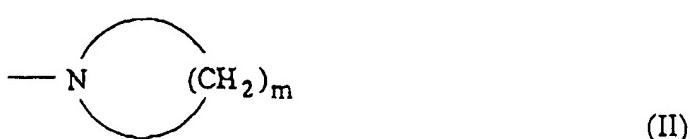


worin X eine direkte Bindung ist;

- 40 oder $-(\text{CH}_2)_n\text{Y}$ - ist, wobei $n = 1, 2$ oder 3 ist und Y eine direkte Bindung, O oder S ist;
 oder $-\text{CH}(\text{R}_{12})\text{Y}$, wobei R_{12} ein Alkyl aus von einem bis sechs Kohlenstoffatomen, ein gesättigter Carboxytring aus von drei bis sechs Kohlenstoffatomen, Phenyl oder Benzyl ist und Y eine direkte Bindung, O oder S ist;
 oder $-\text{C}(\text{R}_{13})=\text{CH}-$, wobei R_{13} Wasserstoff, Alkyl aus von einem bis sechs Kohlenstoffatomen oder Phenyl ist;

45 R_1 und R_2 unabhängig voneinander Wasserstoff, Alkyl von drei bis acht Kohlenstoffatomen, Alkoxyalkyl von drei bis acht Kohlenstoffatomen oder Aralkyl von sieben bis zwölf Kohlenstoffatomen sind;

oder R_1 und R_2 , wenn mit dem Stickstoffatom zusammengenommen, an das sie angebunden sind,
 einen Ring bilden, der durch die Formel II angegeben ist:



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wobei m eine ganze Zahl von drei bis acht ist und der Ring an jedem Kohlenstoffatom durch Hydroxy, Oxo, Alkyl von einem bis drei Kohlenstoffatomen oder Alkoxy von einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzenden Kohlenstoffatomen mit einem aromatischen oder aliphatischen Carboxyrling von sechs Kohlenstoffatomen fusioniert sein kann;

5

oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring von fünf bis acht Ringatomen vervollständigen, der nur Kohlenstoff, Stickstoff und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-Ringatome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe von einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist;

10

oder einen Ring, ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

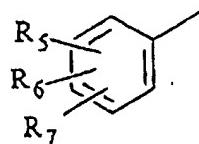
15

R₃ und R₄ unabhängig voneinander an den Cyclohexanring an den 3-, 4-, 5- oder 6-Positionen angebracht sind und unabhängig voneinander Wasserstoff, Hydroxy, Alkyl von einem bis sechs Kohlenstoffatomen oder Alkoxy von einem bis sechs Kohlenstoffatomen sind oder Anbindungspunkte eines Spiro-fünf- oder sechs-gliedrigen heterozyklischen Ringes sind, der ein Sauerstoff- oder Schwefelatom enthält; und

20

A eine Alkylgruppe von fünf bis zwölf Kohlenstoffatomen ist oder ein gesättigter Carboxyrling von drei bis sechs Kohlenstoffatomen ist oder ausgewählt aus Formeln III, IV, V, VI, VII oder VIII ist:

25

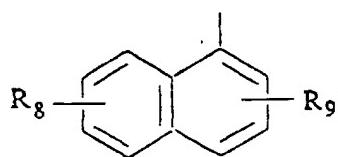


(III)

30

wobei R₅, R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

35

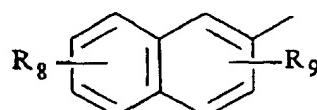


(IV)

40

wobei R₈ und R₉ unabhängig voneinander Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

45

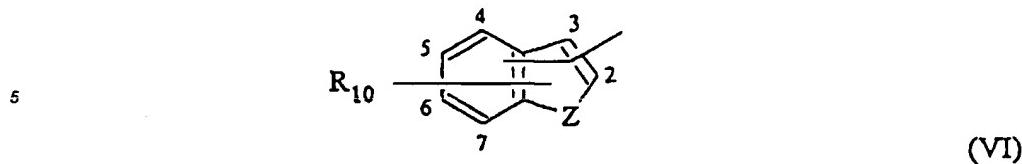


(V)

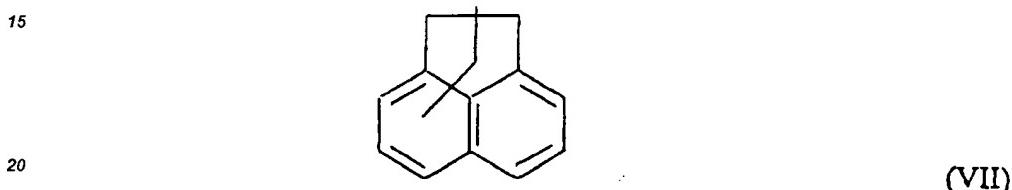
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wobei R₈ und R₉ wie oben definiert sind;

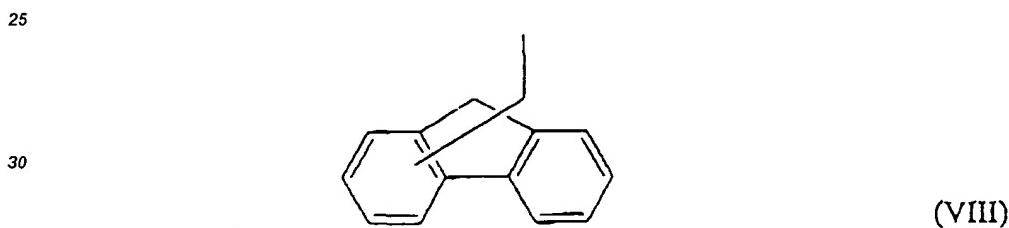
55



10 wobei R₁₀ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl ist; Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Alkyl von einem bis sechs Kohlenstoffatomen ist;

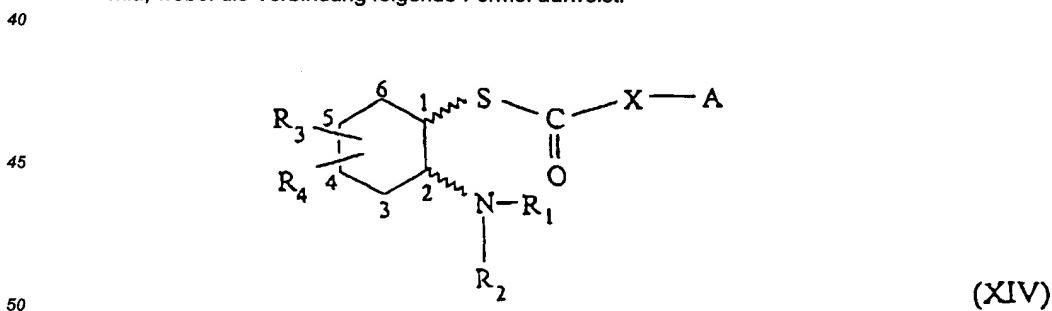


nur wenn X eine direkte Bindung ist;



35 nur wenn X eine direkte Bindung ist;

22. Verwendung eines Enantiomers oder geometrischen Isomers einer Verbindung der Formel XIV oder eines Solvat oder pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikaments zur Behandlung von Arrhythmia, wobei die Verbindung folgende Formel aufweist:



worin X eine direkte Bindung ist;

55 oder -(CH₂)_n-Y- ist, wobei n = 1, 2 oder 3 ist und Y eine direkte Bindung, O oder S ist;
oder -CH(R₁₂)-Y-, wobei R₁₂ ein Alkyl aus von einem bis sechs Kohlenstoffatomen, ein gesättigter Carboxytring aus von drei bis sechs Kohlenstoffatomen, Phenyl oder Benzyl ist und Y eine direkte Bindung, O oder S ist;
oder -C(R₁₃)=CH-, wobei R₁₃ Wasserstoff, Alkyl aus von einem bis sechs Kohlenstoffatomen oder Phenyl ist;

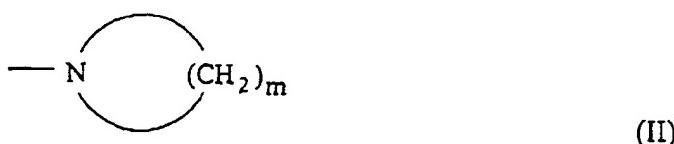
R₁ und R₂ unabhängig voneinander Wasserstoff, Alkyl von drei bis acht Kohlenstoffatomen, Alkoxyalkyl von drei bis acht Kohlenstoffatomen oder Aralkyl von sieben bis zwölf Kohlenstoffatomen sind;

oder R₁ und R₂, wenn mit dem Stickstoffatom zusammengenommen, an das sie angebunden sind,

5

einen Ring bilden, der durch die Formel II angegeben ist:

10



15

wobei m eine ganze Zahl von drei bis acht ist und der Ring an jedem Kohlenstoffatom durch Hydroxy, Oxo, Alkyl von einem bis drei Kohlenstoffatomen oder Alkoxy von einem bis drei Kohlenstoffatomen substituiert sein kann oder an zwei angrenzenden Kohlenstoffatomen mit einem aromatischen oder aliphatischen Carboxytring von sechs Kohlenstoffatomen fusioniert sein kann;

20

oder einen gesättigten monozyklischen Stickstoff heterozyklischen Ring von fünf bis acht Ringatomen vervollständigen, der nur Kohlenstoff, Stickstoff und gegebenenfalls Sauerstoff-Ringatome enthält und wobei der heterozyklische Ring nicht mehr als zwei Stickstoff-Ringatome enthält, wobei der zweite Stickstoff gegebenenfalls mit einer Alkylgruppe von einem bis sechs Kohlenstoffatomen oder einem Phenylring substituiert ist;

25

oder einen Ring, ausgewählt aus 3-Azabicyclo[3.2.2]nonan-3-yl, 2-Azabicyclo[2.2.2]octan-2-yl, 3-Azabicyclo[3.1.0]hexan-3-yl, oder 3-Azabicyclo[3.2.0]heptan-3-yl vervollständigen;

30

R₃ und R₄ unabhängig voneinander an den Cyclohexanring an den 3-, 4-, 5- oder 6-Positionen angebracht sind und unabhängig voneinander Wasserstoff, Hydroxy, Alkyl von einem bis sechs Kohlenstoffatomen oder Alkoxy von einem bis sechs Kohlenstoffatomen sind oder Anbindungspunkte eines Spiro-fünf- oder sechsgliedrigen heterozyklischen Ringes sind, der ein Sauerstoff- oder Schwefelatom enthält; und

35

A eine Alkylgruppe von fünf bis zwölf Kohlenstoffatomen ist oder ein gesättigter Carboxyring von drei bis sechs Kohlenstoffatomen ist oder ausgewählt aus Formeln III, IV, V, VI, VII oder VIII ist:

40

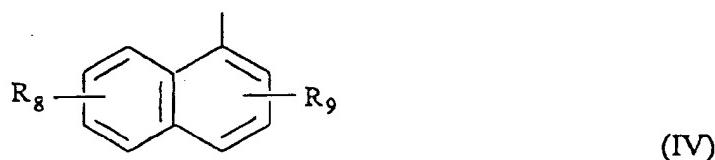


45

wobei R₅, R₆ und R₇ unabhängig voneinander Wasserstoff, Hydroxy, Amino, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

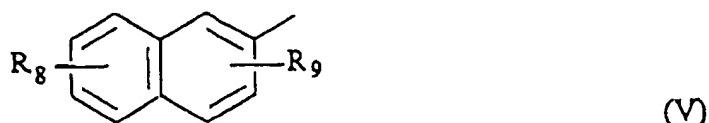
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55



wobei R₈ und R₉ unabhängig voneinander Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl sind;

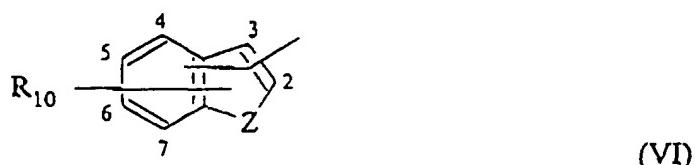
5



10

wobei R₈ und R₉ wie oben definiert sind;

15



20

wobei R₁₀ Wasserstoff, Hydroxy, Fluor, Chlor, Brom, Alkyl von einem bis sechs Kohlenstoffatomen, Alkoxy von einem bis sechs Kohlenstoffatomen oder Aryl ist; Z CH₂, O, S oder N-R₁₁ ist, wobei R₁₁ Wasserstoff oder Alkyl von einem bis sechs Kohlenstoffatomen ist;

25

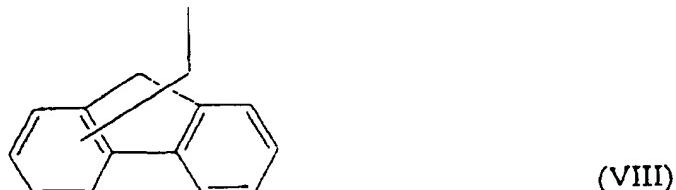
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35

nur wenn X eine direkte Bindung ist;

40



45

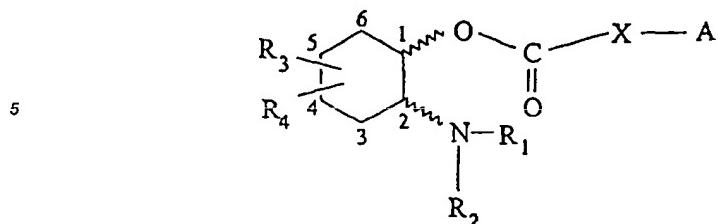
nur wenn X eine direkte Bindung ist;

50

Revendications

- Enantiomère ou isomère géométrique d'un composé chimique ayant la formule I, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

55



(I)

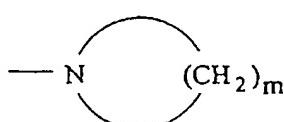
où X est une liaison covalente ;

- 15 ou $-(CH_2)_n-Y$, où $n = 1, 2$ ou 3 et Y est une liaison covalente, O ou S ;
ou $-CH(R_{12})-Y$, où R_{12} est un groupe alkyle comprenant un à six atomes de carbone, un composé homocyclique saturé comprenant trois à six atomes de carbone, phényle ou benzyle, et Y est une liaison covalente, O ou S ;
20 ou $-C(R_{13})=CH-$, où R_{13} est de l'hydrogène, un groupe alkyle comprenant trois à six atomes de carbone ou un phényle ;

R_1 et R_2 sont indépendamment de l'hydrogène, un groupe alkyle comprenant trois à huit atomes de carbone, un alkoxyalkyle comprenant trois à huit atomes de carbone, ou un groupe aralkyle comprenant sept à douze atomes de carbone ;

- 25 ou R_1 et R_2 , considérés ensemble avec l'atome d'azote auquel ils sont attachés,
formant un composé cyclique donné par la formule II :

30



35

(II)

- 40 où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé à n'importe quel atome de carbone par un groupe hydroxy-, oxo- ou alkyle comprenant un à trois atomes de carbone ou par un groupe alkoxy- comprenant un à trois atomes de carbone, ou peut être fusionné, par deux atomes de carbone adjacents, avec un composé isocyclique aliphatique ou aromatique comprenant six atomes de carbone ;

- 45 ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par un cycle phényle ;

- 50 ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabi-cyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

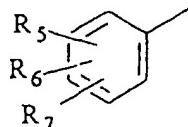
- 55 R_3 et R_4 sont indépendamment fixés au cyclohexane aux positions 3, 4, 5 ou 6, et sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe alkyle de un à six atomes de carbone ou un groupe alkoxy- comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq

ou six membres spiralés contenant un atome d'oxygène ou de soufre ; et

A est un groupe alkyle comprenant cinq à douze atomes de carbone ou est un composé homocyclique saturé comprenant trois à six atomes de carbone, ou est sélectionné à partir des formules III, IV, V, VI VII ou VIII :

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(III)

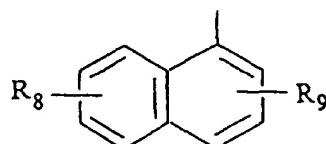
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où R₅, R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle, et quand X est une liaison covalente, l'un au moins d'entre R₅, R₆ et R₇ est remplacé par un groupe hydroxy-, du fluor, du chlore, du brome, du trifluorométhyle, un alkyle comprenant un à six atomes de carbone, ou un aryle, et quand X est -CH=CH-, et que R₁ est R₂ considérés avec l'atome d'hydrogène auquel ils sont fixés, forment une N-phénylpipérazine cyclique et que R₃ et R₄ sont de l'hydrogène, l'un au moins d'entre R₅, R₆ et R₇ est un substitut différent de l'hydrogène ;

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30



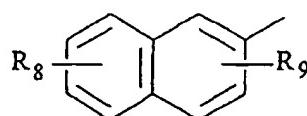
(IV)

35

où R₈ et R₉ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe nitré, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ;

40

45



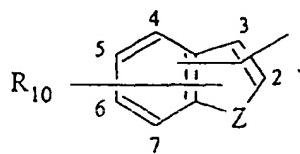
(V)

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où R₈ et R₉ sont définis selon ce qui précède ;

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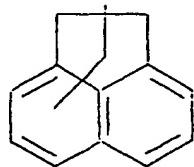


10

où R_{10} est de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du bromé, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ; Z est CH_2 , O, S ou N- R_{11} , où R_{11} est de hydrogène ou un groupe alkyle comprenant un à six atomes de carbone ;

15

20



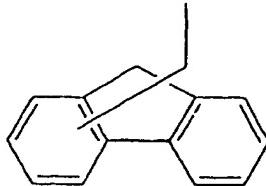
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(VII)

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seulement quand X est une liaison covalente ;

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40

(VIII)

45

seulement quand X est une liaison covalente ;

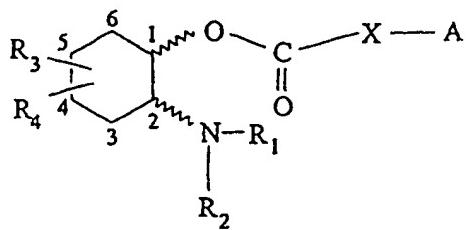
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à condition que, quand X est $-(CH_2)_n-Y-$, et n=1, et Y est une liaison covalente, et quand R_1 et R_2 considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble du pyrrolidinyle cyclique, et R_3 et R_4 sont de l'hydrogène, A ne puisse pas être du thianaphthényl-4.

2. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule I, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

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5



10

(I)

où X est une liaison covalente ;

15

ou $-(CH_2)_n-Y$, où $n = 1$ et Y est une liaison covalente, O ou S ;

ou $-CH(R_{12})-$, où R_{12} est un groupe alkyle comprenant un à six atomes de carbone ;

ou $-C(R_{13})=CH-$, où R_{13} est de l'hydrogène ;

20

R_1 et R_2 sont définis selon la revendication 1 ;

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R_3 et R_4 sont définis selon la revendication 1 ; et

A est défini selon la revendication 1 ;

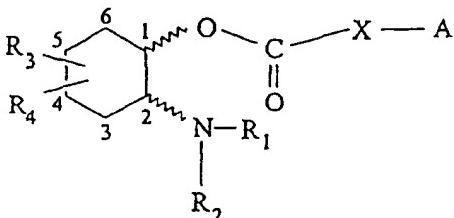
25

à condition que, quand X est $-(CH_2)_n-Y$, et $n=1$, et Y est une liaison covalente, et quand R_1 et R_2 , considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble du pyrrolidinyle cyclique, et R_3 et R_4 sont de l'hydrogène, A ne puisse pas être du thianaphthényl-4.

30

3. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule I, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

35



40

(I)

45

où X est $-(CH_2)_n-Y$, où $n = 1$ et Y est une liaison covalente ou O ;

ou $-CH(R_{12})-$, où R_{12} est un groupe alkyle comprenant un à six atomes de carbone ;

R_1 et R_2 sont définis selon la revendication 1 ;

50

R_3 et R_4 sont indépendamment fixés au cyclohexane aux positions 4 ou 5, et sont indépendamment de l'hydrogène, un groupe alkoxy- comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ; et

A est un groupe alkyle comprenant cinq à douze atomes de carbone ou est un composé homocyclique saturé comprenant trois à six atomes de carbone ou est choisi à partir de :

55

la formule III selon la revendication 1 où R_5 , R_6 et R_7 sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone

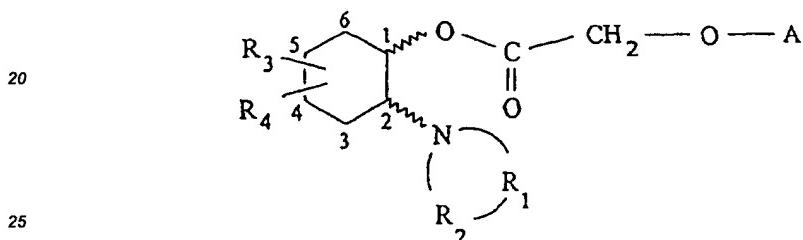
ou de l'aryle ;

ou de la formule IV selon la revendication 1 où R₈ et R₉ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ; ou de la formule V selon la revendication 1 où R₈ et R₉ sont définis selon ce qui précède ;

5 ou de la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ; Z est CH₂, O, S ou N-R₁₁ où R₁₁ est de l'hydrogène ou un groupe alkyle comprenant un à six atomes de carbone ;

10 à condition que, quand X est -(CH₂)_n-Y, et n=1, et Y est une liaison covalente, et R₁ et R₂, considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble du pyrrolidinyle cyclique, et R₃ et R₄ sont de l'hydrogène, A ne puisse pas être du thianaphthényl-4.

- 15 4. Enantiomère ou isomère géométrique d'un composé chimique de la formule IX, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :



(IX)

où R₁ et R₂, quand ils sont considérés ensemble, avec l'atome d'azote auquel ils sont fixés,

35 forment un composé cyclique selon la formule II de la revendication 1, où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé, à n'importe quel atome de carbone, par un groupe hydroxy-, oxo-, alkyle comprenant un à trois atomes de carbone ou alkoxy- comprenant un à trois atomes de carbone, ou peut être fusionné au niveau de deux atomes de carbone adjacents avec un composé isocyclique aliphatic ou aromatique comprenant six atomes de carbone ;

40 ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par un composé cyclique phényle ;

45 50 ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabi-cyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 4- ou 5-, et sont indépendamment de l'hydrogène, un groupe méthoxy- ou sont les points de fixation d'un oxaspirane cyclique à cinq membres ; et

A est un composé homocyclique saturé comprenant trois à six atomes de carbone ou est choisi à partir de :

55 la formule III selon la revendication 1, où R₅ est de l'hydrogène, et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, du méthyle, de l'éthyle, un groupe méthoxy- ou éthoxy- et, parmi R₆ et R₇ l'un au moins est un substitut différent de l'hydrogène ;

ou la formule IV selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;

ou la formule V selon la revendication 1, où R₈ et R₉ sont l'hydrogène ;

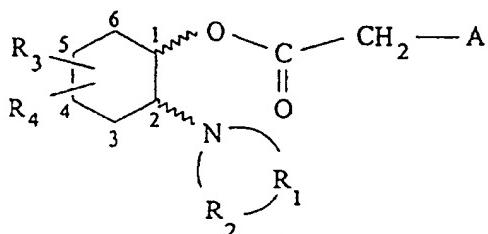
5 ou la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, et Z est CH₂, O, S ou N-R₁₁, où R₁₁ est de l'hydrogène ou du méthyle.

5. Enantiomère ou isomère géométrique d'un composé chimique selon la formule X, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

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(X)

25

où R₁ et R₂ sont définis selon la revendication 4 ;
R₃ et R₄ sont définis selon la revendication 4 ; et

A est un composé homocyclique saturé de trois à six atomes de carbone ou est choisi à partir :

30

de la formule III selon la revendication 1 où R₅ est de l'hydrogène, et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe méthyle, éthyle, méthoxy- ou éthoxy-, et l'un au moins d'entre R₆ et R₇ est un substitut différent de l'hydrogène ;

35

ou de la formule IV selon la revendication 1 où R₈ et R₉ sont de l'hydrogène ;

ou de la formule V selon la revendication 1 où R₈ et R₉ sont de l'hydrogène ;

40

ou de la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, et Z est CH₂, O, S ou N-R₁₁, où R₁₁ est de l'hydrogène ou du méthyle ;

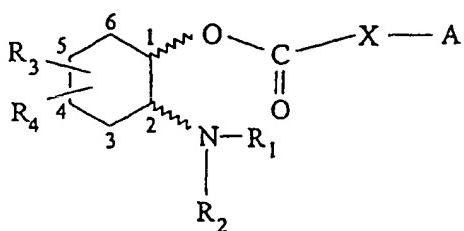
à condition que, quand R₁ et R₂ considérés ensemble et avec l'atome d'azote auquel ils sont fixés, forment un pyrrolidinyle cyclique, et R₃ et R₄ sont de l'hydrogène, A ne puisse pas être du thianaphthényl-4.

45

6. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule I, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

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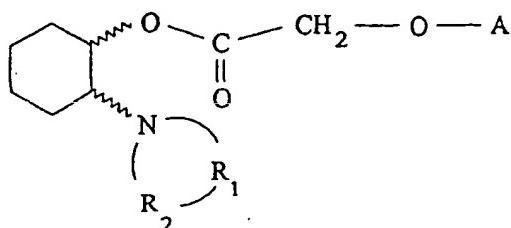


(I)

- 15 où X est une liaison covalente ou -CH=CH- ;
R₁ et R₂ sont indépendamment de l'hydrogène, un groupe alkyle comprenant trois à huit atomes de carbone, un groupe alkoxyalkyle comprenant trois à six atomes de carbone, ou un groupe alkyle comprenant sept à douze atomes de carbone ;
- 20 ou R₁ et R₂, considérés ensemble, avec l'atome d'azote auquel ils sont fixés, forment un composé cyclique ayant la formule II selon la revendication 1, où m est un nombre entier compris entre trois à huit inclus ;
- 25 ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabi-cyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;
- 30 R3 et R4 sont indépendamment fixés au cyclohexane aux positions 4 ou 5, et sont indépendamment de l'hydrogène, un groupe méthoxy- ou sont les points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ; et
- A est un composé homocyclique saturé comprenant 3 à six atomes de carbone ou est choisi à partir de :
- 35 la formule III selon la revendication 1, où R₅ est de l'hydrogène et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, du trifluorométhyle, du méthyle ou de l'éthyle, et l'un au moins d'entre R₆ et R₇ est un substitut différent de l'hydrogène ;
- 40 ou la formule IV selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;
- ou la formule V selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;
- ou la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, et Z est O, S ou N-R₁₁ où R₁₁ est de l'hydrogène ou du méthyle ;
- 45 ou la formule VII selon la revendication 1 quand X est une liaison covalente ;
- ou la formule VIII selon la revendication 1 quand X est une liaison covalente ;
- 50 7. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XI, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

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10



où R1 et R2, considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble un composé cyclique conformément à la formule II de la revendication 1, où m est un nombre entier compris entre trois et huit inclus ; et

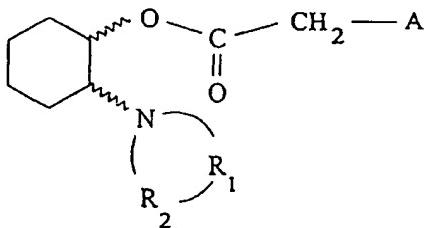
A est choisi à partir de :

- la formule III selon la revendication 1 où R₅ est de l'hydrogène, et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe méthyle, éthyle, méthoxy- ou éthoxy- et, l'un au moins d'entre R₆ et R₇ est un substitut différent de l'hydrogène ;
- ou la formule IV selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ; ou la formule V selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;
- ou la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, et Z est O ou S.

8. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XII, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

35

40



45

(XII)

où R1 et R2, considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble un composé cyclique conformément à la formule II de la revendication 1, où m est un nombre entier compris entre trois et huit inclus ; et

50

A est sélectionné à partir de :

- la formule III selon la revendication 1, où R₅ est de l'hydrogène, et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe méthyle, éthyle, méthoxy- ou éthoxy-, et parmi R₆ et R₇ l'un au moins est un substitut différent de l'hydrogène ;
- ou la formule IV selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;

ou la formule V selon la revendication 1, où R₈ et R₉ sont de l'hydrogène ;

ou la formule VI selon la revendication 1, où R₁₀ est de l'hydrogène, et Z est O ou S ;

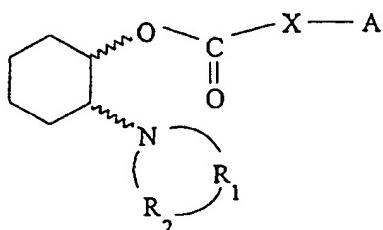
5 à condition que, quand R₁ et R₂ considérés avec l'atome d'azote auquel ils sont fixés forment du pyrrolidinyde cyclique, A ne puisse pas être du thianaphthényl-4.

9. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XIII, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

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15

20



(XIII)

25 où X est une liaison covalente ; trans-CH=CH-, -CH₂- ou -CH₂-O-;

R1 et R2, considérés ensemble, avec l'atome d'azote auquel ils sont fixés, complètent un composé cyclique sélectionné dans la liste suivante : pyrrolidinyde, pipéridinyde, hexahydroazépinyle, morpholinyle, méthylpipérazinyle ou 3-azabicyclo[3.2.2]nonanyle ; et

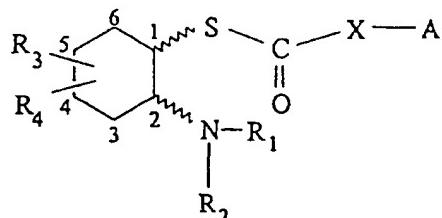
30

A est sélectionné parmi les suivants : cyclohéxyle, dichlorophényle-3,4, bromophényle-4, naphthyle-1, naphthyle-2 ou thianaphthényle-3.

- 35 10. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XIV, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

40

45



(XIV)

50

où X est une liaison covalente ;

ou -(CH₂)_n-Y-, où n = 1, 2 ou 3 et Y est une liaison covalente, O ou S ;

ou -CH(R₁₂)-Y-, où R₁₂ est un groupe alkyle comprenant un à six atomes de carbone, un composé homocyclique saturé comprenant trois à six atomes de carbone, du phényle ou du benzyle, et Y est une liaison covalente, O ou S ;

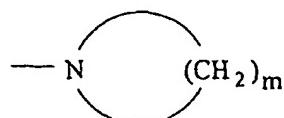
ou -C(R₁₃)=CH-, où R₁₃ est de l'hydrogène, un groupe alkyle comprenant trois à six atomes de carbone ou du phényle ;

R1 et R2 sont indépendamment de l'hydrogène, un groupe alkyle comprenant trois à huit atomes de carbone, un groupe alkoxyalkyle comprenant trois à huit atomes de carbone, ou un groupe aralkyle comprenant sept à douze atomes de carbone ;

5 ou R1 et R2, considérés ensemble, avec l'atome d'azote auquel ils sont fixés,

forment un cycle qui a la formule II :

10



15

(II)

20

où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé sur n'importe quel atome de carbone par un groupe hydroxy-, oxo- ou alkyle comprenant un à trois atomes de carbone ou un groupe alkoxy- comprenant un à trois atomes de carbone, ou peut être fusionné, au niveau de deux atomes de carbone adjacents, à un composé isocyclique aliphatique ou aromatique comprenant six atomes de carbone ;

25

ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par du phényle cyclique ;

30

ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabicyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

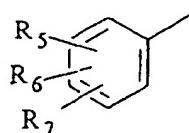
35

R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 3, 4, 5 ou 6, et sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe alkyle comprenant un à six atomes de carbone ou un groupe alkoxy-comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ou de soufre ; et

40

A est un groupe alkyle comprenant cinq à douze atomes de carbone ou est un composé homocyclique saturé comprenant trois à six atomes de carbone, ou est sélectionné à partir des formules III, IV, V, VI VII ou VIII :

45



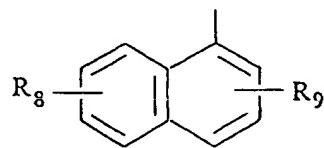
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(III)

55

où R₅, R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle, et quand X est une liaison covalente, l'un au moins d'entre R₅, R₆ et R₇ est un substitut différent de l'hydrogène ;

5



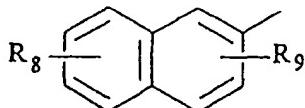
(IV)

10

où R₈ et R₉ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone ou un aryle ;

15

20



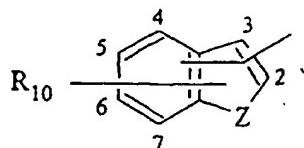
(V)

25

où R₈ et R₉ sont définis selon ce qui précède ;

30

35



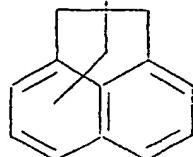
(VI)

40

où R₁₀ est de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ; Z est CH₂, O, S ou N-R₁₁ où R₁₁ est de l'hydrogène ou un groupe alkyle comprenant un à six atomes de carbone ;

45

50

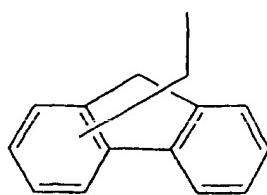


(VII)

55

seulement quand X est une liaison de covalence ;

5



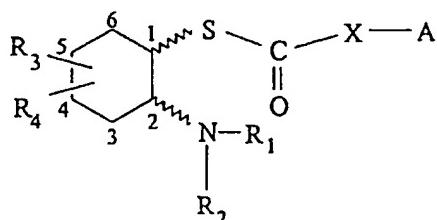
10

(VIII)

seulement quand X est une liaison de covalence.

- 15 11. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XIV, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

20



25

(XIV)

30

où X est une liaison covalente ;
ou -(CH₂)_n-Y-, où n = 1 et Y est une liaison covalente, O ou S ;
ou -CH(R₁₂)-, où R₁₂ est un groupe alkyle comprenant un à six atomes de carbone ;
ou -C(R₁₃)=CH-, où R₁₃ est de l'hydrogène ;

35

R₁ et R₂ sont définis selon la revendication 10 ;

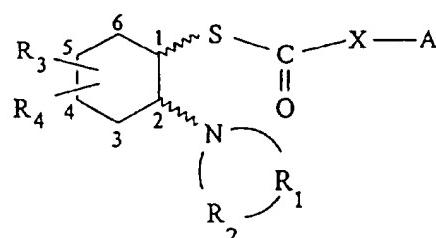
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R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 4, ou 5, et sont indépendamment de l'hydrogène, un groupe hydroxy- comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ; et
A est défini selon la revendication 10.

45

12. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XV, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :

50



55

(XV)

où X est un -CH₂- ou -CH₂O- ;

où R₁ et R₂, considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble un composé cyclique conformément à la formule II de la revendication 10, où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé sur n'importe quel atome de carbone par un groupe hydroxy-, oxo-, alkyle comprenant trois à six atomes de carbone ou alkoxy- comprenant un à trois atomes de carbone, ou peut être fusionné au niveau de deux atomes de carbone adjacents avec un composé isocyclique aliphatic ou aromatique comprenant six atomes de carbone ;

ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par un cycle de phényle ;

ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabicyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 4 ou 5, et sont indépendamment de l'hydrogène, un groupe méthoxy-, ou sont des points de fixation d'un composé cyclique d'oxaspirane à cinq membres ; et

A est un composé homocyclique saturé comprenant trois à six atomes de carbone ou est sélectionné à partir de :

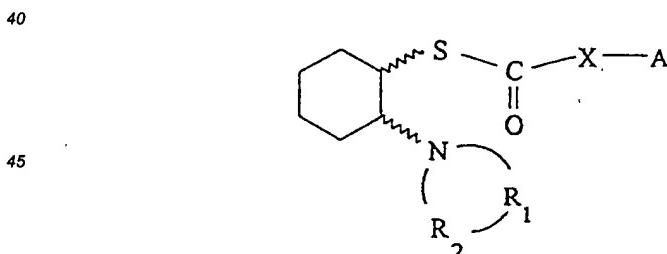
la formule III selon la revendication 10, où R₅ est de l'hydrogène, et R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, du méthyle, de l'éthyle, ou groupe méthoxy- ou éthoxy- ;

ou la formule IV selon la revendication 10, où R₈ et R₉ sont de l'hydrogène ;

ou la formule V selon la revendication 10, où R₈ et R₉ sont de l'hydrogène ;

ou la formule VI selon la revendication 10, où R₁₀ est de l'hydrogène, et Z est CH₂, O, S ou N-R₁₁ où R₁₁ est de l'hydrogène ou du méthyle.

13. Enantiomère ou isomère géométrique d'un composé chimique ayant la formule XVI, ou solvate de ce composé ou sel de ce composé acceptable en pharmacie, ledit composé ayant la formule chimique :



(XVI)

où X est un -CH₂- ou -CH₂O- ;

55 R₁ et R₂, considérés avec l'atome d'azote auquel ils sont fixés, forment ensemble un composé cyclique selon la formule II de la revendication 10, où m est un nombre entier compris entre trois et huit inclus ; et

A est sélectionné à partir de :

la formule III selon la revendication 10 où R5 est de l'hydrogène, et R6 et R7 sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, du méthyle, de l'éthyle, un groupe méthoxy- ou éthoxy- ;

5 ou la formule IV selon la revendication 10, où R₈ et R₉ sont de l'hydrogène ;

ou la formule V selon la revendication 10, où R₈ et R₉ sont de l'hydrogène ;

ou la formule VI selon la revendication 10, où R₁₀ est de l'hydrogène, et Z est O ou S.

10

14. Composé chimique sélectionné dans le groupe composé de :

(±)-trans-[(pyrrolidinyle-1)-2-cyclohéxyle](dichlorophénoxy-3,4)acétate ;

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(±)-trans-[(pyrrolidinyle-1)-2-cyclohéxyle](naphthoxy-1)acétate ;

(±)-trans-[(N-azabicyclo[3.2.2]nonyle)-2-cyclohéxyle](dichlorophénoxy-3,4)acétate ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](dichlorophénoxy-3,4)acétate ;

(±)-trans-[(hexahydroazépinyle-1)-2-cyclohéxyle](dichlorophénoxy-3,4)acétate,

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]benzo[b]thiophenacétate-3 ;

(±)-trans-[(pyrrolidinyle-1)-2-cyclohéxyle](cyclohéxyle)acétate ;

20

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]naphthyle-acétate-1 ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]naphthyle-acétate-2 ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]phénylacétate ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](dichlorophényle-3,4)acétate ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](nitrophényle-4)acétate ;

25

(±)-trans-[(méthyle-4-pipérazinyle-1)-2-cyclohéxyle]naphthylacétate-2 ;

(±)-trans-[(méthyle-4-pipérazinyle-1)-2-cyclohéxyle]naphthylacétate-1 ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]naphthoate-1 ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]benzo[b]thiophenacétate-4 ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](bromophényle-4)acétate ;

30

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]dichlorocinnamate-3,4;

(±)-trans-[(pipéridinyle-1)-2-cyclohéxyle]thiophénoxyacétate ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](naphthyle-1)-2-propionate ;

(±)-(1V, 23, 43, 53)-[diméthoxy-4,5-(prolidinyle-1)-2-cyclohéxyle]benzofuranacétate-2 ;

35

(±)-trans-[[bis-(méthoxyéthyle-2)amino]-2-cyclohéxyle]fluorène carboxylate-9 ;

S-(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]naphthyle thioacétate-1

S-(±)-trans-[[bis-(méthoxyéthyle-2)amino]-2-cyclohéxyle}]bromothiobenzoate-4 ;

(±)-trans-[(diisopropylamino)-2-cyclohéxyle]acénaphthène carboxylate-1 ;

(+)-trans-[(morpholinyle-4)-2-cyclohéxyle]diphénylacétate ;

(±)-trans-[(morpholinyle-4)-2-cyclohéxyle]trifluorométhylbenzoate-3 ;

40

[(pyrrolidinyle-1)-7-oxaspiro-1[4.5]dec-8-yle]naphthylacétate-1 ;

S-(±)-trans-[(morpholinyle-4)-2-cyclohéxyle](diméphoxyphényle-3,4)thioacétate ; et leurs sels acceptables

en pharmacie.

45

15. Mélange comprenant un composé chimique selon l'une quelconque des revendications 1 à 14 combiné à un agent porteur ou diluant acceptable en pharmacie.

16. Composé chimique selon l'une quelconque des revendications 1 - 9 et 14 pouvant être utilisé dans un procédé de traitement de l'arythmie chez un animal à sang chaud.

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17. Composé chimique selon l'une quelconque des revendications 1 - 9 et 14 pouvant être utilisé dans un procédé de blocage des canaux ioniques chez un animal à sang chaud.

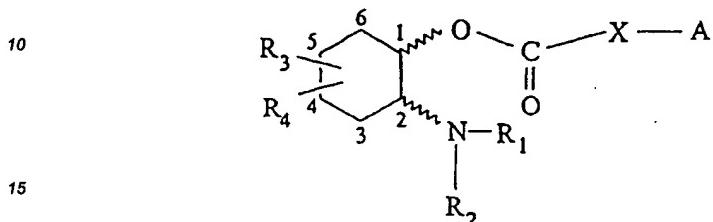
18. Composé chimique selon l'une quelconque des revendications 10 à 13 pouvant être utilisé dans un procédé de traitement de l'arythmie chez un animal à sang chaud.

55

19. Composé chimique selon l'une quelconque des revendications 10 à 13 pouvant être utilisé dans un procédé de blocage des canaux ioniques chez un animal à sang chaud.

20. Composé chimique selon l'une quelconque des revendications 1 à 14 pouvant être utilisé dans un procédé de blocage des canaux ioniques *in vitro*.

21. Utilisation d'un énantiomère ou isomère géométrique d'un composé chimique ayant la formule I, ou d'un solvate de ce composé ou d'un sel de ce composé acceptable en pharmacie, dans la fabrication d'un médicament pour traiter l'arythmie, ledit composé chimique ayant la formule chimique :



(I)

où X est une liaison covalente ;

ou $-(\text{CH}_2)_n-\text{Y}$, où $n = 1, 2$ ou 3 et Y est une liaison covalente, O ou S ;

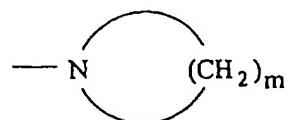
ou $-\text{CH}(\text{R}_{12})-\text{Y}$, où R_{12} est un groupe alkyle comprenant un à six atomes de carbone, un composé homocyclique saturé comprenant trois à six atomes de carbone, du phényle ou du benzyle, et Y est une liaison covalente, O ou S ;

ou $-\text{C}(\text{R}_{13})=\text{CH}-$, où R_{13} est de l'hydrogène, un groupe alkyle comprenant de un à six atomes de carbone ou du phényle ;

30 R_1 et R_2 sont indépendamment de l'hydrogène, un groupe alkyle comprenant trois à huit atomes de carbone, un groupe alkoxyalkyle comprenant trois à huit atomes de carbone, ou un groupe aralkyle comprenant sept à douze atomes de carbone ;

ou R_1 et R_2 , considérés avec l'atome d'azote auquel ils sont attachés,

35 forment ensemble un composé cyclique donné par la formule II :



(II)

45 où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé sur n'importe quel atome de carbone par un groupe hydroxy-, oxo- ou alkyle comprenant de un à trois atomes de carbone ou un groupe alkoxy- comprenant de un à trois atomes de carbone ou peut être fusionné, au niveau de deux atomes de carbone adjacents, avec un composé isocyclique aliphatique ou aromatique comprenant six atomes de carbone ;

50 55 ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant de cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par un composé cyclique phényle ;

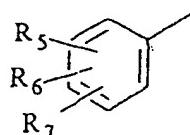
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ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabicyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

5 R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 3, 4, 5 ou 6, et sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe alkyle comprenant un à six atomes de carbone ou un groupe alkoxy-comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ou de soufre ; et

10 A est un groupe alkyle comprenant cinq à douze atomes de carbone ou est un composé homocyclique saturé comprenant trois à six atomes de carbone, ou est sélectionné à partir des formules III, IV, V, VI VII ou VIII :

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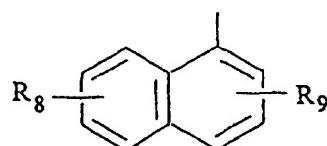
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(III)

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où R₅, R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un groupe aryle ;

30



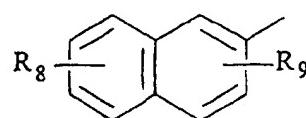
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(IV)

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où R₈ et R₉ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe nitré, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un groupe aryle ;

45



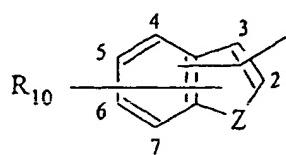
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(V)

où R₈ et R₉ sont définis selon ce qui précède ;

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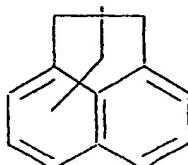
(VI)

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où R_{10} est de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un groupe aryle ; Z est CH_2 , O, S ou $N-R_{11}$, où R_{11} est de hydrogène ou un groupe alkyle comprenant un à six atomes de carbone ;

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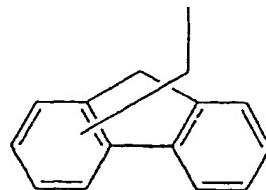
(VII)

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seulement quand X est une liaison covalente ;

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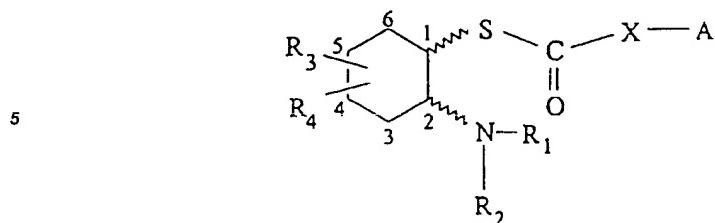
(VIII)

seulement quand X est une liaison covalente.

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- 22.** Utilisation d'un énantiomère ou isomère géométrique d'un composé chimique ayant la formule XIV, ou d'un solvate de ce composé ou d'un sel de ce composé acceptable en pharmacie, dans la fabrication d'un médicament pour traiter l'arythmie, ledit composé chimique ayant la formule chimique :

55



10

(XIV)

- 15 où X est une liaison covalente ;
ou -(CH₂)_n-Y-, où n = 1, 2 ou 3 et Y est une liaison covalente, O ou S ;
ou -CH(R₁₂)-Y-, où R₁₂ est un groupe alkyle comprenant un à six atomes de carbone, un composé homocyclique saturé comprenant trois à six atomes de carbone, du phényle ou du benzyle, et Y est une liaison covalente, O ou S ;
ou -C(R₁₃)=CH-, où R₁₃ est de l'hydrogène, un groupe alkyle comprenant de un à six atomes de carbone ou un phényle ;

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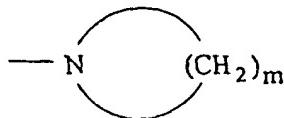
R1 et R2 sont indépendamment de l'hydrogène, un groupe alkyle comprenant trois à huit atomes de carbone, un groupe alkoxyalkyle comprenant trois à huit atomes de carbone, ou un groupe aralkyle comprenant sept à douze atomes de carbone ;

25

ou R1 et R2, considérés avec l'atome d'azote auquel ils sont fixés,

forment ensemble un composé cyclique qui a la formule II :

30



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(II)

- 40 où m est un nombre entier compris entre trois et huit inclus, et ledit composé cyclique peut être remplacé à n'importe quel atome de carbone par un groupe hydroxy-, oxo- ou alkyle comprenant un à trois atomes de carbone ou un groupe alkoxy- comprenant un à trois atomes de carbone, ou peut être fusionné, en deux atomes de carbone adjacents, avec un composé isocyclique aliphatique ou aromatique comprenant six atomes de carbone ;

45

ou complètent un composé hétérocyclique d'azote monocyclique saturé comprenant cinq à huit atomes cycliques, ne contenant que des atomes cycliques de carbone, d'azote et éventuellement d'oxygène, et ledit composé hétérocyclique ne contenant pas plus de deux atomes cycliques d'azote, le deuxième atome d'azote pouvant être remplacé par un groupe alkyle comprenant un à six atomes de carbone ou par un cycle phényle ;

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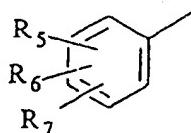
ou complètent un composé cyclique choisi parmi les suivants :3-azabicyclo[3.2.2]nonan-3-yle, 2-azabi-cyclo[2.2.2]octan-2-yle, 3-azabicyclo[3.1.0]hexan-3-yle ou 3-azabicyclo[3.2.0]heptan-3-yle ;

55

R₃ et R₄ sont indépendamment fixés au cyclohexane aux positions 3, 4, 5 ou 6, et sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe alkyle comprenant un à six atomes de carbone ou un groupe alkoxy-comprenant un à six atomes de carbone, ou sont des points de fixation d'un composé hétérocyclique à cinq ou six membres spiralés contenant un atome d'oxygène ou de soufre ; et

A est un groupe alkyle comprenant cinq à douze atomes de carbone ou est un composé homocyclique saturé comprenant trois à six atomes de carbone, ou est sélectionné à partir des formules III, IV, V, VI VII ou VIII :

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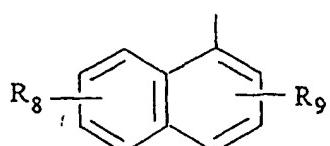
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(III)

15

où R₅, R₆ et R₇ sont indépendamment de l'hydrogène, un groupe hydroxy-, un groupe aminé, du fluor, du chlore, du brome, un groupe nitré, du trifluorométhyle, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un aryle ;

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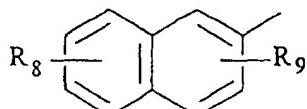
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(IV)

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où R₈ et R₉ sont indépendamment de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone ou un groupe aryle ;

35



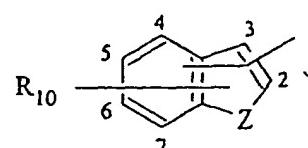
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(V)

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où R₈ et R₉ sont définis selon ce qui précède ;

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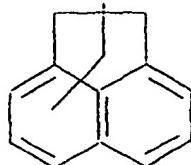
(VI)

où R₁₀ est de l'hydrogène, un groupe hydroxy-, du fluor, du chlore, du brome, un groupe alkyle comprenant

un à six atomes de carbone, un groupe alkoxy- comprenant un à six atomes de carbone, ou un groupe aryle ; Z est CH₂, O, S ou N-R₁₁ où R₁₁ est de l'hydrogène ou un groupe alkyle comprenant un à six atomes de carbone ;

5

10



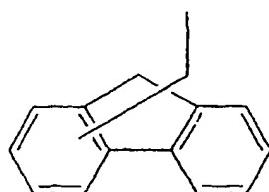
(VII)

15

seulement quand X est une liaison de covalence ;

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(VIII)

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seulement quand X est une liaison de covalence.

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